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Volume 76

Alan R. Katritzky

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Tautomerism of Heterocycles: Five-Membered Rings with Two or More Heteroatoms

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Preface

Volume 76 of *Advances in Heterocyclic Chemistry* is concerned with heteroaromatic tautomerism. This subject was first dealt with in a comprehensive manner in Volumes 1 and 2 of *Advances in Heterocyclic Chemistry,* which appeared in 1963 and 1964. This material was updated in a special supplementary volume, which appeared in 1976. Subsequently, much further information has become available and we have now attempted to bring the whole subject up-to-date.

The present volume commences with an introductory chapter authored by Drs. J. Elguero (Madrid, Spain), A. R. Katritzky, and O. V. Denisko (both of the University of Florida, U.S.A.) and deals with the many advances in the methods of investigation of tautomeric equilibria and the general conclusions that can now be drawn regarding the subject.

The second chapter concerns the tautomerism of five-membered ring systems with a single heteroatom concentrating mainly on pyrroles, furans, and thiophenes. It is authored by Professor W. Friedrichsen and Dr. T. Traulsen (University of Kiel, Germany) together with Drs. J. Elguero and A. R. Katritzky.

The final chapter in the present volume is concerned with the tautomeric equilibria of five-membered rings containing two or more heteroatoms and has been written by Professors V. I. Minkin and A. D. Garnovskii (Rostov University, Russia), together with Drs. J. Elguero, A. R. Katritzky, and O. V. Denisko.

Our survey of heteroaromatic tautomerism will be completed in three further chapters, two of which will appear in Volume 77 of our series covering the tautomerism of (i) rings with three, four, and seven or more members and (ii) two or more fused five- or six-membered heterocyclic rings. The final chapter dealing with the tautomerism of six-membered monocyclic ring systems will appear in a subsequent volume.

ALAN R. KATRITZKY

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 76

Prototropic Tautomerism of Heterocycles: Heteroaromatic Tautomerism—General Overview and Methodology

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I. Introduction

In 1963 one of us, together with J. M. Lagowski, published in Volumes 1 and 2 of *Advances in Heterocyclic Chemistry* four chapters [63AHC(1), p. 312, p. 341; 63AHC(2), p. 3, p. 28] which comprise the first attempts at a complete survey of prototropic tautomerism of heteroaromatic compounds. In 1976 two of the present authors, together with C. Marzin and P. Linda, published a monograph dealing comprehensively with the subject as a supplementary volume of *Advances in Heterocyclic Chemistry* (76AHCS1).

As was emphasized in these two overviews and has been many times since [e.g., 89JA7; 91H(32)329], tautomeric equilibria are important. It is impossible to correctly interpret the detailed mechanisms of reactions of tautomeric heterocycles without knowing the dominant tautomeric structure. Equally, it is impossible to correctly interpret the biological activity and function of potentially tautomeric heterocycles without representing them in their correct structure. Nowhere is this more graphically illustrated than in the case of the nucleic acid helix, where the hydrogen bonding between the nucleic acid bases depends vitally on the tautomeric structures in which these bases exist. In 1963 there was scant regard for trying to depict the structures of potentially tautomeric heterocycles in their dominant form. The situation has since improved, but the strictures that we made in the introduction to our 1976 monograph unfortunately still apply:

> Difficulties . . . that have been increased because of the unfortunate tendency of some otherwise intelligent and reasonable chemists to represent tautomeric heterocyclic compounds by other than the predominantly existing tautomers. As it hoped to make clear during the course of this book the information presently available enables us to predict with a good chance of success the predominant tautomeric structure for nearly all the heterocyclic compounds that we are likely to encounter. Surely *this* is the structure by which they should be named and more importantly depicted in reaction schemes. It is essential that trained heterocyclic chemists should use the correct structure and this is even more important so that good habits be engendered in non-chemists. It seems very difficult to expect that biochemists and biologists should have any understanding of the subject at all if we do not write down what we mean.

The present chapter is the first part of a joint project in which we are trying to update the 1976 review with an account of the progress that has been made in the subject over the past 2 decades or so.

II. General Discussion

Decalogue of Tautomerism

I. Do not confuse mesomerism and tautomerism.
II. Do not ignore a tautomer even if it is a minor one.
III. Two identical tautomers can be in mobile equilibrium.
IV. The name should correspond to the most abundant tautomer.
V. Tautomerism is concerned with kinetics as well as with equilibria.
VI. Many types of tautomerism exist in addition to prototropic.
VII. There is a close relationship between tautomerism and physical state.
VIII. Tautomerism occupies at least a tridimensional space: physical state, thermodynamic *vs* kinetic approach, and proton *vs* other migrating entities.
IX. Tautomerism and aromaticity are intimately linked.
X. An understanding of tautomerism is vital for understanding chemical reactivity.

Papers dealing with tautomerism that have appeared since 1975 can be divided in two main groups. A small proportion of them are studies devoted explicitly to tautomerism; such papers (see, for instance, P. J. Taylor [96JCS(P2)2263]) are usually based on a clear understanding of the problem. The larger proportion of papers dealing with tautomerism do so in an oblique way. Here, two situations are found, depending on whether the result is consistent or not with the generally accepted situation regarding the tautomerism of already studied heterocycles of similar structure. Leaving aside some minor errors, this situation corresponds to the conclusions of the previous edition of "The Tautomerism of Heterocycles" (76AHCS1). If the result is consistent, e.g., that aminopyridines are predominantly in the amino form, they need little proof and *require little comment*. On the other hand, if the result contradicts the paradigm, e.g., a conclusion that an imino tautomer

is more stable than the amino one, then it deserves to be discussed at length and *proof must be presented*. Moreover, an explanation should be provided based on either general physical-organic chemical considerations or on theoretical calculations. For a new paper on tautomerism to be significant it must report either the use of original methodology [see, for instance (97JA6336)] or results in some underrepresented areas, such as temperature effects on the tautomeric equilibrium constant in the gas phase leading to reliable ΔS values and rates of proton transfer between tautomers.

A. Principal Types of Tautomerism

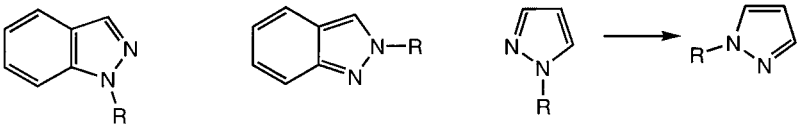
The types of tautomerism are well summarized in our previous monograph.

Tautomerism occurs when two isomers exist in mobile equilibrium with each other. Isomers are molecules having the same atomic composition. Note that for isomers to be considered tautomers two conditions have to be met:

1. The interconversion must be relatively easy, i.e., the energy barrier separating the tautomers must not be too high. No fixed limit exists, but with ΔG of less than 25 kcal they would certainly be considered as tautomers, whereas with an energy barrier of about 40 kcal they would not be considered as tautomers. However, frequently such energy barriers can be lowered by using a suitable catalyst.
2. Both of the tautomers must coexist, i.e., the energy difference between them must not be so high that one of the forms is not present. A pK_T of around 20 is the sort of limit that could be taken here.

The phenomenon of tautomerism comprises many different types of which the prototropic tautomerism that we consider here is only one. Prototropic tautomerism exists when the two tautomers differ only in the position of a proton (this is, of course, an approximation; there are other differences between two tautomers, for example, in precise bond lengths). Other important types of tautomerism include the following: (1) anioniotropy, where the two tautomers differ only in the position of an anion, which moves from one place to another in the molecule; (2) cationiotropy, where the two tautomers differ in the position of a cation (other than a proton), which moves from one place to another in the molecule; (3) ring-chain tautomerism; and (4) bond-valence tautomerism.

There has been some interest in comparing prototropic tautomerism to other equilibria where the migrating entity is not the proton. A significant



SCHEME 1

contribution to this field is a series of publications by Beak [(76AHCS1, p. 74; 80JOC1347) and references therein] using "methyltropic" equilibria to obtain important information relevant to prototropic tautomerism and heteroaromaticity. From comparisons of the equilibria of azoles and benzazoles for a series of *N*-substituents (H, CHROH, CMe_2OH, COMe, $SiMe_3$) other authors concluded that such variation had but a little effect on the position of tautomerism [78JCS(P2)99]. For instance, in the case of indazole, the 1-substituted tautomer (R = H) or "isomer" (R ≠ H) **1a** is more stable than the 2-R indazole **1b,** irrespective of the nature of R.

When comparing the equilibria for R = H with R ≠ H, the following two aspects must be considered:

1. Prototropic tautomerism differs from all other types (methyltropy, metallotropy, acylotropy, halogenotropy, etc.) because the proton is very small, and therefore insensitive to steric effects, and also that it forms hydrogen bonds (HBs), which can considerably affect both the equilibrium and the rate of the process.
2. The activation energy to tautomer interconversion is lower for H than for other groups, with the exception of some metals (fluxionality). For instance, the 1,2-migration aptitude in pyrazole (**2a** → **2b**) has the following approximate activation energies:

$\Delta G^{\ddagger}$	C_6H_5	CH_3	COR	SiR_3	GeR_3	**H**	HgR_2	SnR_3
(kcal mol^{-1})	> 40	35	30	25	20	10-15	10	5

The above value for R = H corresponds to an intermolecular process,[1] either assisted by the solvent (in solution) or by other NH-pyrazole molecules (in solution and in the solid state) while metal migrations are probably intramolecular (the bigger the metal, the easier) and those of COR correspond (for R = NHR') to a dissociation–recombination mechanism. Minkin [quoted in 96MI(15)339] suggests that a tautomeric process should

[1] The *ab initio* calculated 1,2-H intramolecular migration in azoles has a barrier of 50 kcal mol^{-1} (Section III,G).

have an activation barrier <25 kcal mol^{-1} and the tautomeric equilibrium should be established in a short time period ($<10^{-4}$ s).

Deuterium-labeling and mass spectrometry prove that the mechanism of the thermal O to N rearrangement of 4-alkoxypyridines to *N*-alkyl-4-pyridones is intermolecular (88CS347).

B. Nomenclature

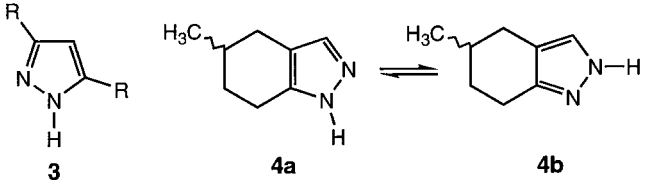
Generally the name of a compound should correspond to the most stable tautomer (76AHCS1, p. 5). This is often problematic when several tautomers have similar stabilities, but is a simple and reasonable rule whose violation could lead to naming phenol as cyclohexadienone. Different types of tautomerism use different types of nomenclature. For instance, in the case of annular tautomers both are named, e.g., 4(5)-methylimidazole, while for functional tautomerism, usually the name of an individual tautomer is used because to name all would be cumbersome. In the case of crystal structures, the name should reflect the tautomer actually found; therefore, 3-nitropyrazole should be named as such (97JPOC637) and not as 3(5)-nitropyrazole.

C. Existence of Individual Tautomers

Any doubt about the existence of individual tautomers is now long past: some tautomers can be crystallized separately (desmotropy), and others can be observed simultaneously in the same crystal (Section V,D,2); in summary, tautomers are not intrinsically different from isomers. Maybe it is worth mentioning that even two *identical* tautomers can *differ*. This is the case for the two intramolecular hydrogen-bonded (IMHB) enol tautomers of acetylacetone and for many NH-azoles: they correspond to a double-well profile for the proton transfer with both wells having the same energy (autotrope).

D. Mechanism and Rate of Tautomeric Change

It is well accepted that tautomerism relates to the equilibrium between two or more different tautomers; e.g., it corresponds to determining if the structure of a compound is, for instance, a pyridone or an hydroxypyridine. The kinetic aspects are often neglected and when the tautomeric equilibrium constant, K_T, is equal to 1 (e.g., for imidazole), the problem may seem



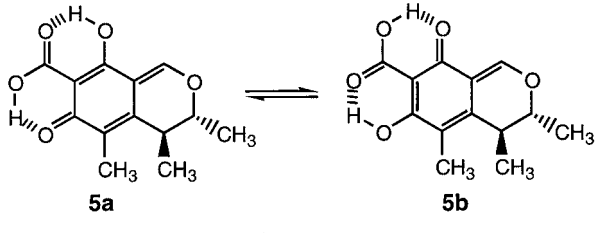
SCHEME 2

devoid of interest. However, there are two reasons to consider degenerate (autotrope) tautomeric equilibria: (1) for kinetic studies using NMR spectroscopy, such equilibria are specially well suited to determine activation barriers since they correspond to equal populations; and (2) $K_T = 1$ due to symmetry reasons is true in the gas phase and in solution because, in the solid state, asymmetry in the crystal packing can lead to an apparent $K_T \neq 1$; for instance, for 3,5-disubstituted pyrazoles **3** with identical substituents (Scheme 2) [95JHC451, 97JCS(P2)1867].

A situation found in very few cases in crystals, but very important for the understanding of the mechanism of tautomeric change, is when two different tautomers are present in the same unit cell (Section V,D,2) and they are rapidly equilibrating. This is the case for 5-methyl-4,5,6,7-tetrahydroindazole (**4**) where tautomers **4a** and **4b** exist in a 53/47 ratio (Scheme 2) (97CEJ121).

Although not a heteroaromatic compound, the case of citrinin studied by Destro and Luz ([97JPC(A)5097] and references therein) is so significant that it deserves mention here. Citrinin exists in the crystal as a mixture of the *p*-quinone **5a** and *o*-quinone **5b** tautomers (Scheme 3). The equilibrium is temperature dependent and by using ^{13}C CPMAS NMR (Section VI,F) and, more remarkably, X-ray crystallography, the authors were able to determine the ΔH and ΔS values (the rate is extremely fast on the NMR time scale, $>10^6\ s^{-1}$).

In Section VI,G, which deals with NMR dynamic studies, the results concerning rate constants in solution and in the solid state are discussed. In the gas phase, no activation barriers have been reported but the fact that tau-



SCHEME 3

tomers can be at equilibrium has been demonstrated several times. Equilibrium of the protomers in the vapor phase was established by Beak *et al.,* who demonstrated that, in the case of 2-hydroxypyridine/2-pyridone tautomerism, the UV relative absorptions (Section VII,C) are temperature dependent [76JA171] as are the corresponding infrared intensities of the OH and NH stretching vibrations (Section VII,B) (92JPC1562). Photoelectron spectroscopy (Section VII,D) has been used to demonstrate that the two tautomers of benzotriazole 1-oxide, which can be crystallized separately, (desmotropy) yield the same PE spectrum (that corresponding to 1-hydroxybenzotriazole) when vaporized [95SA(A)1801]. In cases when the tautomerization implies a C-H bond breaking, the rates are slow enough to be measured by conventional kinetic methods [97JCS(P2)2761].

E. Influence of External Factors on the Equilibrium Position of a Tautomeric Mixture

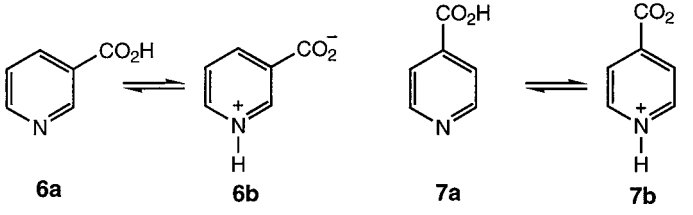
In this section we summarize some results on phase and temperature effects. A useful introduction on the effect of solvent in heterocyclic tautomerism is given in Reichardt's book (90MI1, p. 98). The three main effects (excluding pressure) that affect the position of the equilibrium, i.e., substitution, solvent, and temperature, are usually treated as independent although it is known that this assumption is false. See [80AQ(C)211] for a study concerning azido/tetrazole tautomerism in thiazolo[3,2-*d*]tetrazoles in which these three effects are treated simultaneously. Alarcón *et al.* [94JCS(P2)1067, 96JCS(P2)2293] have pointed out that when studying substituent effects on the tautomeric equilibrium it is necessary to remember that solvent effects (Onsager-type) also change with the substituents and that both terms can cancel.

Solvent studies have continued to appear since our earlier review (76AHCS1); thus, one of us described the results obtained with pyridones and reported that Kosower's Z ($\log K_T = a + bZ$) yields results slightly better than Reichardt's E_T [76JCS(P2)1428]. Beak, for the same compounds, rationalized the data with an equation, $\Delta G^{\circ}_{s} - \Delta G^{\circ}_{v} = a\,O + b\beta + c\alpha$, where the solvent (s) and the gas-phase (v) free-energy differences are equated to the sum of three terms, the Onsager function O $[(\epsilon - 1)/(2\epsilon + 1)]$, and the Kamlet–Abboud–Taft parameters for the basicity (β) and acidity (α) of the solvent. In this way, it is possible to determine the position of the equilibrium in the gas phase for species that are not volatile (80JOC1347). Freyer discussed the more complicated case of pyrazolin-5-ones (three tautomers) using Gutmann donor (DN) and acceptor (AC) descriptors of solvent properties. He found that the proportion of CH and

OH tautomers vary linearly with DN while the proportion of the NH tautomer depends on AC [83JPR(325)238]. Experimental data on the effect of solvents on the annular tautomerism of 5-aryltetrazoles [84JCS(P2)721] and 1,2,3-triazole [89JCS(P2)1903] have also been reported. All these results can be treated using the three parameter equation of Kamlet–Abboud–Taft (π^*, α, β) and then mutually compared. Inclusion in a host can be considered as a solvent effect, although a very specific one; Toda has demonstrated that this considerably modifies the equilibrium position (86NKK1746; 87CL2317; 88CL1061).

The equilibrium between neutral **a** and zwitterionic **b** forms in the case of nicotinic **6** and isonicotinic **7** acids has been studied by Hallé in mixtures of DMSO and water (from 0 to 100%) (Scheme 4). The position of the equilibrium is very sensitive to the composition of the solvent and for more than 80% of DMSO, the **a** form essentially dominates the equilibrium in solution (96CJC613). An analysis of their data shows a perfect linear relationship ($r^2 = 1$) between the ln K_T of the two acids and moderate linear relationships between ln K_T and the percentage of DMSO. Johnston has studied the equilibrium 2-hydroxypyridine/2-pyridone in supercritical fluids (propane at 393 K and 1,1-difluoroethane at 403 K) (89JPC4297). The equilibrium constant K_T (pyridone/hydroxypyridine) increases four-fold for a pressure increase of 40 bar in 1,1-difluoroethane.

Some temperature effects on K_T (or populations) have been reported; all reach the same expected conclusion that the populations become more alike (or K_T approaches 1) when the temperature increases. Table I summarizes some results concerning different pyrazolin-5-ones: 1-phenyl-3-acetylamino (**8**) (74BSF291); 1-phenyl-3-methyl (**9**) [83JPR(325)238]; and 1,3-dimethyl (**10**) and 1,3-diphenyl (**11**) [99JCS(P2)211]. 2-Substituted-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-ones (**12**) present an equilibrium enamine **12a**/imine **12b** (Scheme 5) which has been determined, for five derivatives, at eight temperatures (between 50° and 150°C). Nevertheless, calculations (97JHC773) (not reported by the original authors) show significant variations in the percentages as determined by ^{1}H NMR or in the temperature; an example is reported in Table I.



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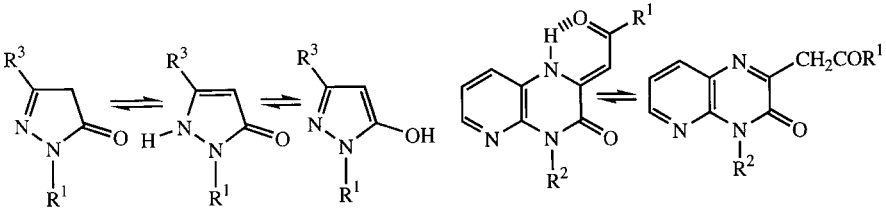


8, $R^1 = C_6H_5$, $R^3 = CH_3CONH$
9, $R^1 = C_6H_5$, $R^3 = CH_3$
10, $R^1 = R^3 = CH_3$
11, $R^1 = R^3 = C_6H_5$

SCHEME 5

TABLE I
TEMPERATURE EFFECTS ON K_T (VALUES IN KILOCALORIES PER MOLE)

Compound	K_T (tautomers)	Solvent	T (°C)	ΔG	ΔH	$T\Delta S$
8	CH/NH+OH	DMSO	303	0.75	3.0	2.1
9	CH/NH+OH	DMF	303	0.5	2.0	1.5
9	CH/NH+OH	THF	183	0.0	0.0	0.0
10	CH/NH+OH	DMSO	303	1.0	2.8	1.8
11	CH/NH+OH	DMSO	303	1.1	2.2	1.1
12	imine/enamine	DMSO	323	2.3	12.1	9.8

III. Theoretical Methods

A. INTRODUCTION

Probably the most important change since the publication of our monograph "The Tautomerism of Heterocycles" (76AHCS1) is the explosive development of computational studies of tautomerism. Today it would be possible to write a book devoted to "The Tautomerism of Heterocycles" using only calculated properties. When the level of calculations is sufficiently high (for instance, MP2/6-31+G**) (97MI1), the precision and accuracy of such theoretical calculations can often exceed most experimental results. Another advantage of computational methods is that they can calculate the energies of the species that are not experimentally available.

All indications are that computation facilities (better programs, faster computers) will continue to progress at a steady pace and render such a book easier to write and more comprehensive. However, there are two neg-

ative aspects to such a restricted approach. First, the extraordinarily rapid evolution of computational chemistry will quickly make such a book obsolete. We already find this problem when commenting on theoretical results: which should be quoted, the first calculation or the higher level one? Some important molecules presenting tautomerism, for instance the nucleic bases, have been the subject of an almost continuous series of calculations (ca. one report per month). We have decided to report in this chapter *ab initio* calculations *exclusively;* if a molecule like the protein crambin (642 atoms) can be optimized at the HF/4-21G level [98JPC(A)2246], most molecules involved in tautomerism should be small enough to be calculated, avoiding the approximations of semiempirical methods.

The second aspect is more fundamental. It is related to the very nature of chemistry (quantum chemistry is physics). Chemistry deals with fuzzy objects, like solvent or substituent effects, that are of paramount importance in tautomerism. These effects can be modeled using LFER (Linear Free Energy Relationships), like the famous Hammett and Taft equations, with considerable success. Quantum calculations apply to individual molecules and perturbations remain relatively difficult to consider (an exception is general solvation using an Onsager-type approach). However, preliminary attempts have been made to treat families of compounds in a variational way [81AQ(C)105].

Since the domain explored will always be a very small part of the possible cases of tautomerism, it is essential to have general rules for families of compounds, substituents, and solvents. This "chemical" approach is maintained in this chapter, although the importance of the calculations is recognized. The following discussion begins with calculation of tautomeric equilibrium constants, followed by the combined use of theoretical calculations and experimental results (an increasingly expanding field) and ends with the calculations of the mechanisms of proton transfer between tautomers.

B. Equilibrium Constants, Temperature, and Solvent Effects

There is an evolution with time; the older calculations correspond to isolated molecules in the gas phase without any corrections, the more recent ones include solvent effects, with different approximations, and also some corrections, like ZPE (zero-point energy correction). The contributions of some authors to the understanding of tautomerism have been significant. Some of their contributions are collected in Table II.

The main theoretical studies can be divided into five fields (Table III). We discuss an example of each field in the gas phase and in solution, conclud-

TABLE II
THEORETICAL CALCULATIONS: MAIN AUTHORS CONTRIBUTIONS

Authors	References
L. Adamowicz, A. Les	89CPL(161)73, 89JPC7078; 90JPC7021; 93MI(224)13, 93MI(228)1; 94CPL(225)265, 94MI(231)61
J. Catalán, J. L. G. de Paz	88JA4105; 89JA7348, 89JCC426, 89NJC151; 94JOC2799, 94MI(19)32; 96JCS(P2)57; 97JCS(P2)101
I. H. Hiller	83JA3568; 89CPL(161)185; 90JCS(P2)329, 90JPC5499, 92JCS(P2)1681; 92JCS(P2)2151, 92JOC4434; 93JA2352, 93JCS(P2)331, 93JCS(P2)861, 93JCS(P2)1771; 95THE(331)147
J. Leszczynski	90CPL(173)371; 93JPC3520; 94THE(311)37; 95STC281; 97JPC(A)4753; 98JPC(A)2357
F. J. Luque, M. Orozco	90JOC753; 95JA1378, 95JOC969, 95JPC3084; 96JA6811, 96JOC5964, 96JPC4269; 97MI(11)153, 97TCA(96)105; 98JPC(B)5228
G. La Manna	84THE(110)183; 89THE(188)199; 93THE(287)127; 95JMS(330)431

ing with a comment about temperature effects, i.e., the calculation of the entropy pertaining to the tautomeric equilibrium.

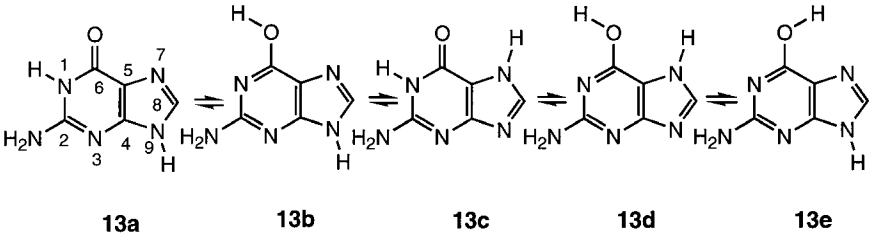
1. Nucleic acids and related compounds. The tautomerism of guanine **13** (Scheme 6) (76AHCS1, p. 523) is one of the most complicated cases to study theoretically because there are four important tautomers (**13a**–**13d**) plus a rotamer (**13e**) to consider (not considering improbable imino forms). The first calculations, although carried out at very high level (MP2, MP4, DFT), considered only tautomers **13a** (the most stable in solution) and **13b** and concluded that in the gas phase they are of similar energy [89CPL(161)185, 95THE(331)147]. A complete study which considers the five possibilities was later published (96JA6811); at the highest level of the calculations (MP4/6-311++G^{**}//MP2/6-31G^{*}), the stabilities of the five forms relative to **13a** are (in kilocalories per mole): **13a** (0) > **13c** (0.2) > **13b** (1.1) > **13e** (1.8) > **13d** (4.4). These authors also considered solvent effects (water), which were calculated *ab initio,* and used Monte Carlo free energy perturbations. Tautomerism of guanine is notably changed upon solvation: only **13a** (0) and **13c** (1–2) should be present in water. The most recent paper [98JPC(A)2357] contains information about the calculated energy barrier (see Table VI). For similar studies on thiouracil see 89JCS(P2)1507.

2. Aminoacids and other molecules of biological interest. Histamine **14,** like guanine, has nonstandard numbering: tautomers **14a** and **14b** are called N(3)H and N(1)H instead of 4- and 5-aminoethyl, like other imidazoles. In

TABLE III

THEORETICAL CALCULATIONS: MAIN TOPICS EXPLORED (LISTED BY REFERENCE NUMBER)

Nucleic acids and related compounds	Aminoacids and other molecules of biological interest	Pyridones and other six membered compounds (functional tautomerism)	Annular tautomerism of azoles and benzazoles	Pyrazolines and other five-membered compounds (functional tautomerism)
79IJQ(6)475; 88JA2353; 89CPL(161)185; 89JCS (P2)1507, 89JPC7078; 90JCS(P2)329, 90JOC753; 93JPC3520; 94CPL(225)265, 94THE(311)37; 95JPC9702, 95STC281, 95THE(331)147; 96CPH(211)147, 96JOC5964, 96JST(376)375, 96THE(369)93; 97IJQ(62)489, 97JPC(A)4753, 97JPC(A)8309, 97JST(413-414)271, 97MI(11)153, 97SA(A)1211; 98JPC(A)2357	79MI(14)9; 81CJC3232; 83IJQ(10)293; 83IJQ(10)293; 84JMC1531; 85JA6689; 87JCC142, 87JCPB633; 97IC6287, 97JOC9240, 97TCA(97)59	81IJQ(8)359; 82IJQ(22)1041; 83JA3568; 84THE(110)183; 85JA7569, 85THE(120)73; 89CPL(161)73, 89THE(188)199; 90CPL(171)475, 90CPL(173)371, 90JPC7021, 90THE(206)295; 91JCC17; 93JCS(P2)861, 93JPC46, 93THE(287)127; 94H1957, 94T2405; 95JMS(330)431; 96IJQ(57)721, 96JPC16141; 97THE(401)1, 97THE(419)97	87IJQ(31)405, 87THE(152)331; 88ACS(A)500, 88JA4105; 89JA7348, 89JCC426, 89NJC151; 90JOC5683; 93JA2465; 94JOC2799, 94NJC269, 94THE(304)45, 94THE(306)115; 95T7045, 95THE(337)9; 96CPL(262)689, 96JCS(P2)57; 97JCS(P2)101, 97JPC(A)7885, 97JPOC637, 97STC189; 98JCS(P2)2497; 99AX(B)ip, 99H227, 99H355	82JPR(324)827, 89JOC3553; 92STC231; 94MI(19)32, 94STC225, 96ZOB1341; 97JCS(P2)1783, 97JPC(A)3769, 97ZN(B)535; 97ZN(B)535; 98JST(447)71, 98NJC1421
		Solvent effect studies		
92JOC4434; 95IJQ(56)615, 95JA1378, 95JOC969, 95JPC3084; 96JA6811 96THE(365)63; 97JPC(A)4753	96THE(369)137	84CPH(85)397; 92BCJ1002; 93JCS(P2)331; 94MI(231)61; 95IJQ(56)645 95JPC15062; 96ACR298, 96JPC4269, 96JPC16141; 97MI(42)17	88THE(165)115; 89BBA(993)134; 90JPC5499; 97JPC(A)7885, 97TCA(96)105	92JCS(P2)2151; 93JA2352; 93JCS(P2)1771
		Temperature effect studies		
		93MI(224)13; 93MI(228)1	94JOC2799	99JCS(P2)211



13a **13b** **13c** **13d** **13e**

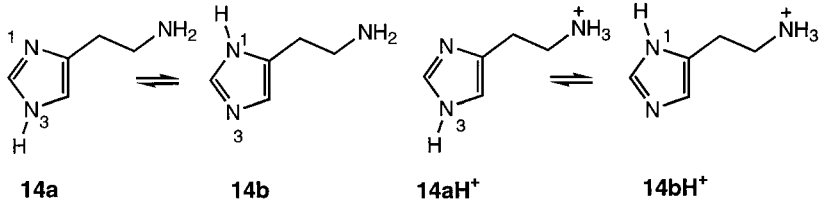
SCHEME 6

the solid state, the structures of **14b** and **14aH**$^+$ have been found [84JMC1531]. The importance of the molecule in medicinal chemistry prompted Richards, Wallis, and Ganellin to carry out STO-3G calculation on both the neutral molecule (75% of **14b**) and the cation (>99.99% of **14aH**$^+$) [79MI(14)9]. Topiol reported calculations at the same level on guanylhistamine (83IJQ(10)293) and on histamine itself (84JMC1531). His results for histamine were in agreement with Richards *et al.* Increasing the level of the calculation to 3-21G//STO-3G yielded almost identical energies for both neutral tautomers, **14a** and **14b,** while cation **14aH**$^+$ is 13 kcal mol^{-1} more stable than **14bH**$^+$ (87JCC142; see also 87JCPB633). More recently, the tautomerism of histamine was explored both in the gaseous state and in aqueous medium at 6-31G//6-31G (93JA1450) and MP2 levels [96THE(369)137]. In aqueous medium the N(3)H tautomers **14b** and **14bH**$^+$ (with a strong intramolecular HB) are the most stable (Scheme 7).

3. Pyridones and other six-membered compounds (functional tautomerism). The pyridone[2]/hydroxypyridine tautomerism (76AHCS1, p. 87), especially 2-pyridone (**15a**)/2-hydroxypyridine (**15b**), has received more attention from theoreticians than any other example of tautomerism, probably in part because it is a simple model for biologically important molecules such as thymine, cytosine, and uracil (Scheme 8).

Hillier (83JA3568) calculated the tautomerism **15a**/**15b** at the 6-31G**/3-31G level and found good agreement of the calculated enthalpy with the experimental value in the gas phase (**15b** being the more stable by less than 1 kcal mol^{-1}). Both Hillier (83JA3568) and Fraga (85JA7569) calculated that 4-hydroxypyridine **16b** is more stable than 4-pyridone **16a** in the gas phase. Kwiatkowski, Bartlett, and Person (88JA2353), using many-body perturbation theory (MBPT) over 6-31G*//3-31G SCF calculations, estimated the difference in favor of **15b** to be 1 kcal mol^{-1}. According to Adamowicz, the value raises to 3.5 kcal mol^{-1} at 0 K, still in favor of **15b,** using coupled cluster calculations [89CPL(161)73], a value overestimated according to Moreno and Miller [90CPL(171)475] [a good summary of the

[2] Although the correct name is pyridinone in most papers it is reported as pyridone.

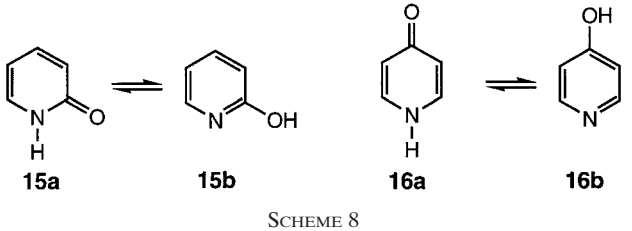


SCHEME 7

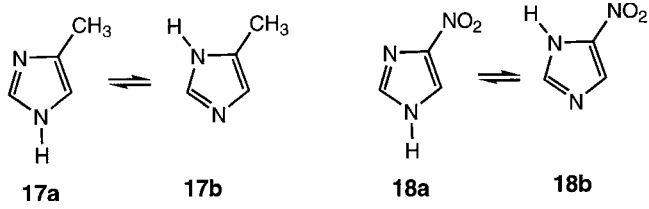
different calculations is given by Fabian (91JCC17)]. Hillier *et al.* [93JCS(P2)861], using TZV2P basis sets and electron correlation at the QCISD(T) level, reproduced the exact same experimental value for the energy difference between **15a** and **15b** in the gas phase (0.7 kcal mol^{-1}, in favor of the hydroxy tautomer **15b,** see 93JPC46).

This system has also been a benchmark for studying solvent effects. Some preliminary studies mainly concerned water [81IJQ(8)359, 85JA7569, 85THE(120)73]. Gao (96ACR298 and references therein) describes the hybrid quantum and molecular mechanical simulations approach to solvent effects in organic chemistry. One of the examples concerns the effect of water and chloroform on the 2- (**15**) and 4-pyridone (**16**) tautomerism. The gas-phase preference of the hydroxy tautomers is predicted to be dramatically reversed in water in favor of the oxo forms by -4.6 and -3.7 kcal mol^{-1} for **15a** and **16a.** Two subsequent papers on this subject include one by Luque *et al.* [96JPC4269] on the effect of chloroform solution, which reproduces the experimental findings exactly, and another by Boyd [96JPC16141] including different solvents (cyclohexane, chloroform, and acetonitrile), which opens the way to a real understanding of tautomeric equilibria in solution.

4. Annular tautomerism of azoles and benzazoles [the nonaromatic tautomers of imidazole **17,** 2H and 4(5)H have been calculated at the MP2/6-31G* level to be about 15 kcal mol^{-1} less stable than the 1H tautomer (95JOC2865)]. We present here the case of 4(5)-substituted imidazoles, different from the histamine, histidine, and derivatives already discussed. By analogy with these histamines, 4-methylimidazole **17a** is often named "distal" [N(τ)H] and 5-methylimidazole **17b,** "proximal" [N(π)H] (Scheme 9).



SCHEME 8



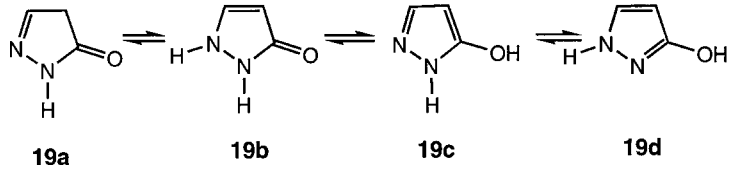
SCHEME 9

No less than six studies were devoted to this compound. After a preliminary paper concluded that **17b** is more stable in the gas phase than **17a** by 0.8 kcal mol^{-1} [87IJQ(31)405], all subsequent publications found the 4-methyl tautomer the most stable by (all values in kilocalories per mole): 1.25 (4-31G//STO-3G) [90JA1303], 0.33 (MP2/6-31G**//6-31G) [89BBA(993)134], 0.16 (MP2/6-31G*) [94THE(304)45], 0.69 (MP2/6-311++G**//MP2/6-31G*) [97JPC(A)7885], and 0.7 (MP4/6-311+G**) [97TCA(96)105]. The last two values should be considered the most reliable. A similar value (0.67 kcal mol^{-1} in favor of the 4-ethyl) has been reported in the case of 4(5)-ethylimidazole [92MI(43)139]. The tautomerism of imidazoles bearing aromatic and heteroaromatic substituents at position 4(5) has been calculated at the 3-21G*/AM1 level [94THE(306)115]: in all cases, the 5-substituted tautomer is favored. On the contrary, calculations (6-31G) show that both tautomers of 4(5)-nitroimidazole **18** have similar energies (89NJC151).

In most of these studies, the tautomerism has also been calculated in the condensed phase. Thus, 4-methylimidazole (**17a**) is predicted to continue to be the most stable tautomer in water, with ΔG only slightly less than in the gas phase [89BBA(993)134; 90JA1303; 97JPC(A)7885, 97TCA(96)105]. In the case of 4(5)-nitroimidazole (**18**), the calculated equilibrium constant (**18a**)/(**18b**) changes from $K_T = 1$ in the gas phase to $K_T = 99$ in aqueous solution (89NJC151). This different behavior of **18** as compared to **17** is due to the fact that both tautomers of **17** have similar dipole moments (**17a** 3.52, **17b** 4.01 D) [94THE(304)45], while the dipole moments are very different for **18a** (8.75 D) and **18b** (4.24 D) (89NJC151).

5. Pyrazolinones and other five-membered compounds (functional tautomerism). These studies have often used the most simple but rather experimentally neglected pyrazolin-5-one **19.** Its four tautomers are called CH **19a,** NH **19b,** 5-OH **19c,** and 3-OH **19c** (Scheme 10) [76AHCS1, p. 313].

A preliminary study of the above equilibrium, using 4-31G//MNDO calculations and including thermal and solvation energies [82JPR(324)827], was significantly improved by subsequent calculations. Enchev increased the level of the calculations to 4-31G//STO-3G and considered four other



SCHEME 10

tautomers corresponding to isopyrazole and pyrazolenine structures, all of them much higher in energy (92STC231); for the four "classical" tautomers he found the following order of stability (the differences in energy in kilocalories per mole relative to **19a** are in parentheses): **19a** (0.0) < **19c** (0.13) < **19d** (7.88) < **19b** (16.22). The first high-level calculations (MP4/6-31G**//3-21G) were those of Hillier *et al.* (93JA2352); in the gas phase, he found **19a** (0.0) < **19d** (2.4) < **19c** (5.9) < **19b** (8.9) and in water **19c** < **19b** < **19d** < **19a,** which has to be compared with the experimental result (from pK_a measurements, Section V,A) **19b** < **19d** < **19c** < **19a.** The level was further increased by Shäfer *et al.* (MP2/6-311+G**//MP2/6-31G**), who found that **19c** (0.0) < **19a** (2.3) < **19c** (4.1) < **19b** (7.5) in the gas phase (94JPC11353); in water, the calculated order of energies is **19d** (0.0) < **19b** (0.8) < **19c** (3.6) < **19a** (3.7), which is in better agreement with experimental results than Hillier's calculations. Water solvent effects on the equilibrium between the four tautomers of **19** (including two rotamers for **19d**) were reevaluated by Luque and Orozco [97TCA(96)105]. DFT calculations on 3(5)-ethoxycarbonyl-5(3)-hydroxypyrazole (including a dimer) agree that the 3-hydroxy-5-ethoxycarbonyl tautomer is the most stable; this is the tautomer which is found in the crystal (Section V,D,2) [98JST(447)71].

N-Substituted pyrazolin-5-ones have only three and *N*-substituted pyrazolin-3-ones only two tautomers, since now the corresponding **19c** and **19d** structures are isomers. The calculations involved: 1-methylpyrazolin-5-one (PM3/6-31+G*, anions and cations), 1-phenyl-3-methyl-2-pyrazolin-5-one (DFT, radical reactions) [97JPC(A)3769], and 1-(2′,4′-dinitrophenyl)-3-methyl-2-pyrazolin-5-one [B3LYP/6-31G* and the crystal structure (Section V,D,2)] (98NJC1421).

6. The description of the behavior of a tautomeric equilibrium over a wide range of temperatures requires the calculation of ΔS in addition to ΔH, which is the value usually obtained. This is important when dealing with techniques such as FVP (Flash Vacuum Pyrolysis), which operates at very high temperatures (500–700°C) [99JCS(P2)211]. The experimental results (Section II,E) suggest that these effects are generally weak and calculations generally agree with this observation, for instance in the case of pyrazolinones [82JPR(324)827; 94JPC11353; 99JCS(P2)211]. The effect of

temperature on the water solvates of 4-hydroxypyridine and 2-hydroxypyrimidine has been studied by Les and Adamowicz [93MI(224)13, 93MI(228)1]. Recently, a high-level calculation of the four tautomers of pyrazolo[3,4-*d*]pyridazine including ZPE, the effect of water solvation, and TDS contribution (very small) was published [97MI(42)17].

C. Heats of Formation and Gas-Phase Basicity

Although not essentially different from the previous section, we have collected here theoretical publications aimed indirectly to the calculation of the equilibrium constant, either through the heats of combustion or through acid–base equilibria.

Concerning the enthalpies of formation, which are routinely obtained from semiempirical calculations such as MNDO or AM1, they are difficult to calculate *ab initio* and, in general, only relative values are calculated for compounds of the same molecular composition by means of isodesmic reactions (98JCP692). This precludes carrying out a calculation for the two tautomers and comparing the calculated values with the experimental ones. Some authors have used Hess's law to overcome this difficulty [97JPC(A)283].

TABLE IV

Theoretical Calculations of Proton Affinities and pK_a Values

Substrate	Method	Result	Tautomer	Reference
4(5)-Methylimidazole	4-31G//STO-3G	PA	Both	90JA1303
4(5)-Nitroimidazole	3-21G//3-21G	PA	Both	89CJC1666
histamine	6-31G//6-31G	PA	1H	93JA1450
3(5)-Methylpyrazole	4-31G//STO-3G	PA	Both	90JA1303
3(5)-Nitropyrazole	6-31G//6-31G	PA	3-Nitro	92JOC3938
3(5)-Nitropyrazole	MP2/6-31G**	PA	3-Nitro	97JPOC637
3(5)-Aminopyrazole	6-31G//6-31G	PA	3-Amino	92JOC3938
3(5)-Diazoniopyrazole	6-31G//6-31G	PA	3-N_2^+	95JCS(P2)379
1,2,4-Triazole	6-31G*//6-31G	PA	1H	86JPC5597
Tetrazole	6-31G*//6-31G	PA	—[a]	86JPC5597
Indazole	STO-3G//STO-3G	PA	1H	83T2851
Indazole	MP2/6-31G**//6-31G*	pK_a	1H	94JPC10606
7-Azaindole	STO-3G//STO-3G	PA	1H	83T2851
7-Azaindole	STO-3G//STO-3G	pK_a	1H	84THE(107)263
Pyrazolinones	6-31+G*//6-31+G*	PA	CH	97ZN(B)535
2-Pyridone	DFT	PA	NH/OH	94T2405
2-Aminopyrimidine	6-31G*/6-31G	PA	Amino	95MI(40)407

[a] No conclusion can be drawn because the two tautomers yield, on protonation, two different conjugated acids.

The calculation of the proton affinities (PA) for a pair of tautomers and the comparison with experimental data [generally from ICR measurements (Section VII,F)] has been the subject of a series of publications with increasing sophistication (Table IV). Such calculations concerning the annular tautomerism of azoles and benzazoles have been reviewed [87AHC(41)187].

D. Dipole Moments and Microwave Spectroscopy

A combination of experimental dipole moments either in solution (Section V,C) or, preferably, in the gas phase (Section VII,A) with calculated dipole moments can be used to determine the tautomeric preference [remembering that the additive property is the scalar μ^2 (76AHCS1, p. 33)]. Basis set effects on the dipole moments are relatively small, but electron correlation effects are much larger (between SCF and MP2; dipole moments differ by an average of 0.5 D and a maximum of 0.7 D in purine derivatives [96THE(366)185]). The experimental values (MW) in the case of 1,2,3-triazole (1H 4.38 D, 2H 0.22 D) are in reasonable agreement with calculated ones (1H 4.95 D, 2H 0.52 D) using a double zeta basis [88ACSA(A)500]. In the case of tetrazole, only the 2H-tautomer **22b** has a calculated dipole moment (MP4/6-31G*//MP2/6-31G*, 2.31 D) that agrees with the experimental gas phase value [95THE(337)9]. In the case of indazole, the experimental value (MW: 1.76 D) [92JSP(155)1] corresponds to the 1H-tautomer (MP2/6-31G**//MP2/6-31G**: 1.92 D); the 2H tautomer has a calculated dipole moment of 2.72 D [96JCS(P2)57]. The MW rotational constants are an even better test; in the case of indazole, the experimental values, $|a| = 1.9251$, $|b| = 1.9508$, and $|c| = 0.0$ [92JSP(155)1], and the calculated values for 1*H*-indazole, $|a| = 1.9687$, $|b| = 1.9598$, and $|c| = 0.0$, and for 2*H*-indazole, $|a| = 3.2943$, $|b| = 0.1186$, and $|c| = 0.0$, leave no doubt about the tautomer present in the gas phase. In the case of benzotriazole, the experimental value (MW: 4.3 D) [93JSP(161)136] corresponds to the 1H-tautomer (MP2/6-31G**//MP2/6-31G**: 4.24 D) (94JOC2799), but it was an error to conclude that the 2H-tautomer was absent in the gas phase [93JSP(161)136] because its low calculated dipole moment (0.38 D) (94JOC2799) prevented its observation (Section VII,A). A table with recommended dipole moments and polarizabilities for the different tautomers of a series of purine derivatives (purine, hypoxanthine, allopurinol, xanthine, and alloxanthine) is available from MP2/6-31G** calculations [96THE(366)185].

Calculated (6-31G**//3-21G) dipole moments were also compared with the corresponding experimental values determined in benzene at 25°C

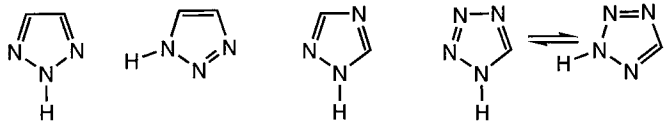
(95BSB383) for 3(5)-phenyl-5(3)-methylpyrazole and its *N*-methyl derivatives.

E. Electronic, Photoelectronic, and IR Spectra

Concerning the electronic spectra (UV and visible, Section VII,C), the situation concerning *ab initio* calculations is well summarized by Broo and Holmén [97JPC(A)3589]. These authors compare the INDO/S-CI and CIS/6-31G* methods (in the case of adenine, they also carried out CASPT2 calculations) for calculating the electronic spectra ($n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions) of DNA and RNA bases (purine, adenine, guanine, thymine, uracil, and cytosine). Their main conclusions are: (1) the use of accurate geometries (in their case MP2/6-31G*) is very important since the calculated spectral properties are sensitive to the ground-state geometry; (2) it is possible to simulate the spectra in water solution by calculating the corresponding base-H_2O complexes (specific solvation) and adding nonspecific solvent effects through self-consistent reaction fields (SCRF); and (3) the tautomerism (for instance, the oxo-enol tautomerism of cytosine or the 7H $\rightleftharpoons$ 9H tautomerism of guanine **13**) can be studied by comparing the calculated spectra with the experimental one.

In photoelectron spectroscopy (PES) it is a widespread practice to carry out calculations simultaneously with the use of fixed forms (Section VII,D). Palmer, in a series of significant studies of the PES of azoles and benzazoles [77JST(40)191; 78JST(43)33, 78JST(43)203], usually limited himself to compare the experimental spectrum with the *ab initio* calculated one. This is probably the origin of his conclusion that benzotriazole is exclusively in the 1H-tautomeric form, which has been proved erroneous (94JOC2799). In subsequent papers, Palmer combined theoretical calculations with experimental studies of model compounds [81ZN(A)1246; 87CPH(111)249]; in this way he demonstrates the predominance of 2*H*-1,2,3-triazole **20a,** 1*H*-1,2,4-triazole **21** and 2*H*-1,2,3,4-tetrazole **22b** in the gas phase (Scheme 11).

Vibrational spectroscopy (IR and Raman, Section VII,B) is a field where theoretical calculations have revolutionized the method; two groups have made essential contributions to prototropic tautomerism:



Scheme 11

(1) Kwiatkowski and Lesczcynski and (2) Nowak, Adamowicz, Smets, and Maes. Within the harmonic approximation, *ab initio* methods yield very accurate frequencies for the fundamental vibrations (normal coordinate calculations) although in most cases the values need to be scaled (scaling factor 0.9 to 0.98 depending on the theoretical method used). The comparison with the experimental spectrum suffers for the following reasons: (1) most tautomeric compounds are studied in solution while the calculated spectrum corresponds to the gas phase; (2) combination, overtone, and Fermi resonance bands are not computed; and (3) calculations are much less accurate for absolute intensities than for frequencies. This last problem can be partially overcome by recording the complementary Raman spectrum. Some representative publications are shown in Table V.

TABLE V

THEORETICAL CALCULATIONS ON INFRARED SPECTRA

Substrate	Method	Tautomer	Reference
2-Pyridone	6-31G**	Both, OH pred.	92JPC1562
2-Pyridone	6-311G**	Both	94THE(312)201
2-Pyridone	DFT(B3LYP)	Both, OH pred.	96JST(376)325
2-Thiopyridone	DFT(B3LYP)	Both, SH pred.	96JST(376)325
3-Hydroxypyridine	6-31++G**	OH[a]	95JPC14967
4-Hydroxypyridine	6-31++G**	OH[a]	95JPC14967
Pyridazine-3-thione	3-21G*	Thione	91JPC2404
Pyrimidine-4-thione	3-21G*	Both, SH pred.	91JPC2404
2-Aminopyridine-HCO_2H	6-31G	Complex[b]	97NKK100
4-Aminopyridine	6-31++G**	NH_2[a]	95JPC6387
4-Aminopyrimidine	6-31++G**	NH_2[a]	95JPC6387
Uracil	Gas phase	Dione	97CPL(269)39
Cytosine	3-21G	Both	88JA8319
Cytosine	6-31G**	Both	92SA(A)811
Cytosine	DFT(B3LYP)	Several	96JPC941
Thymine	Gas phase	Dioxo	97CPL(269)39
Thiocytosine	DFT(B3LYP)	Several	96JPC941
Purine	6-31++G**	N(9)H/N(7)H	97JST(410/411)397
Adenine	Gas phase	Amino	97CPL(269)39
1-Methyladenine	6-31++G**	N(9)H	96SA(A)383
1-Methyladenine	6-31++G**	N(9)H, imino	97JST(410/411)397
3-Methyladenine	6-31++G**	Amino, N(7)H, imino	97JST(410/411)397
N-Methyladenine	6-31++G**	Amino N(9)H	97JST(410/411)397
9-Aminoacridine	DFT(B3LYP)	Amino/imino	97JPC(A)283
1,2,3-Triazole	MP2/6-31G*	1H/2H	91JPC3123
3-Nitro-1,2,4-triazolone	DFT(B3LYP)	1H, one	96JST(384)87

[a] Comprises calculations of the supermolecules (one water molecule).
[b] The neutral complex is more stable than the 2-aminopyridinium formate complex.

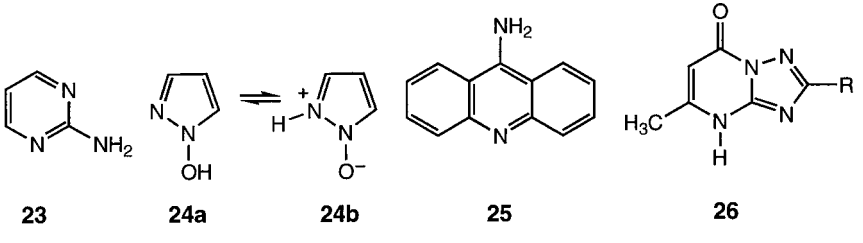
F. NMR Chemical Shifts

Ab initio calculations of absolute shieldings (which can be transformed in chemical shifts by calculating, at the same level, the references used for each nuclei) is a very successful approach to tautomerism (Section VI,C). The three most used computational methods are the GIAO (gauge including–or invariant–atomic orbital), the IGLO (individual gauge for localized orbitals), and the LORG (local orbitals-local origins) (97JA8699; 99CR293 and references therein). Thus, ^{1}H, ^{13}C, ^{15}N, and ^{17}O absolute shieldings have been calculated for benzotriazole and its 5(6)- and 4(7)-nitro derivatives [94JST(327)321]. These values were used to assign the different signals and to demonstrate that 1H/3H tautomerism occurs in benzotriazoles. The ^{1}H, ^{13}C, and ^{15}N shieldings of aminopyrimidines, for instance **23,** showed only amino tautomers (GIAO) (97JA8699) (Scheme 12). The ^{13}C, ^{15}N, and ^{17}O shieldings of 1-hydroxypyrazole **24** showed mainly 1-hydroxy **24a** (GIAO) [98THE(453)255]. The ^{1}H and ^{13}C spectra of 9-aminoacridine **25** were not conclusive for the amino/imino tautomerism (GIAO) [97JPC(A)283]. Facelli has carried out LORG calculations on the ^{17}O isotropic chemical shieldings of 2-pyridones, including pyridone **15** itself, and compared them with experimental ^{17}O chemical shifts (92JPC7895). Kleinpeter [97JST(435)65, 97MI(3)375] has calculated, using the GIAO approximation, the ^{13}C and ^{15}N chemical shifts of 2-substituted 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones **26** (four tautomers). The tautomerism of 3(5)-fluoropyrazoles has been determined by comparing experimental and calculated ^{19}F chemical shifts [99H355].

No *ab initio* coupling constants calculations related to tautomerism are available; however, semiempirical calculations using, for instance, INDO have been reported [83THE(94)163].

G. Proton Transfer and Activation Barriers

Discussion of topics corresponding to proton transfer occurring in the excited state are included under "Fluorescence Spectroscopy and Excited



23 **24a** **24b** **25** **26**

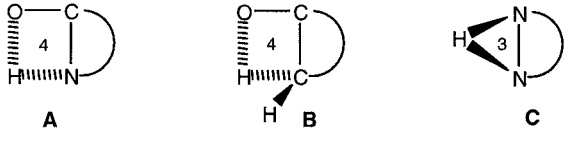
Scheme 12

TABLE VI
THEORETICAL CALCULATIONS OF PROTON TRANSFER BARRIERS

Substrate	Method	Solvent molecules	High barrier[a] (kcal mol^{-1})	Reference
2-Pyridone **15**	3-21G	None[b]	49	84CPL(107)330
2-Pyridone **15**	3-21G	Dimer[c]	11	84CPL(107)330
2-Pyridone **15**[d]	3-21G	$2H_2O$	13.5	84JCS(CC)1310
2-Pyridone **15**[e]	STO-3G	$1H_2O$	23.4	85THE(120)73
2-Pyridone **15**	CISD+ZPE	None[b]	38.5	90CPL(171)475
2-Pyridone **15**	CCSD(T)+ZPE	None[b]	32.4	93JCC1429
2-Pyridone **15**	GC-LDA[f]	None[b]	33.5	95IJQ(56)645
2-Pyridone **15**	DFT(B3LYP)	None[b]	35.3	95JPC15062
2-Pyridone **15**	DFT(B3LYP)	1 H_2O	12.5	95JPC15062
2-Pyridone **15**	DFT(B3LYP)	2 H_2O	13.5	95JPC15062
Guanine **13**	MP2/6-31G**	None[b]	36	98JPC(A)2357
Tetrazole	QCISD(T)/6-311+G**	None[b]	49.5	93JA2465
Pyrazole	DFT(B3LYP)	None[b]	47.3	98JCS(P2)2497
3(5)-Hydroxypyrazole[g]	MP2/6-31G**	None[b]	50	94JPC11353
3(5)-Hydroxypyrazole[h]	MP2/6-31G**	None[b]	70	94JPC11353
3(5)-Hydroxypyrazole[i]	MP2/6-31G**	None[b]	50	94JPC11353

[a] High barrier is the barrier from the most stable tautomer to the less stable one.
[b] Intramolecular proton transfer.
[c] SCF + MBPT + ZPE calculations [92THE(277)313] and MP2/6-31+G** calculations [97JPC(B)9199] of the three possible dimers (oxo-oxo, oxo-hydroxy, and hydroxy-hydroxy).
[d] Plus effect of bulk solvent [87JCS(P2)617].
[e] See also 86AQ(A)194.
[f] Nonlocal density gradient corrections (GC)-local spin density (LDA) approximation.
[g] Annular tautomerism (between 3- and 5-hydroxy tautomers).
[h] Functional tautomerism (between 5-OH and CH tautomers).
[i] Functional tautomerism (between NH and 3-OH tautomers).

State Proton Transfer" (Section VIII). The general problem of intramolecular proton transfers includes tunneling paths (91JPC10457). The most relevant results are reported in Table VI.



All the intramolecular proton transfers correspond to three TS‡'s of types **A, B,** and **C.** Case **A** is that of 2-pyridone (**15a** → **15b**), guanine **13** (**13a** → **13b**, **13c** → **13d**), and 3-hydroxypyrazole **19** (**19b** → **19d**). Case **B** is that of **19a** → **19c,** whereas case **C** is that of 1,2-proton shifts in azoles like pyrazole and tetrazole. All these processes have very high energies and

probably never occur. On the contrary, TS‡'s assisted by dimerization (pyridines), trimerization [pyrazoles (Section VI,G)] or by one or two water molecules have low activation barriers consistent with experimental results. A theoretical study [DFT(B3LYP)] of the tautomerization of pteridines and purines relevant to the reaction mechanism of the molybdenum hydroxylase xanthine oxidase has been carried out *in vacuo* and with the Kirkwood/Onsager reaction field of the solvent [97ICA(263)87]. The assistance by proton acceptor molecules on the 1,2-proton shift in N*H*-tetrazoles lowers the barrier from 50 to 28 kcal mol^{-1} [98JCS(P2)2671].

IV. Chemical vs Physical Methods for the Study of Tautomerism

No section corresponding to "The Chemical Methods Used to Study Tautomerism" (76AHCS1, p. 12) has been included in the present chapter because it is now obsolete, but a section about "Tautomerism and Reactivity" has been added (Section X). The classification and the precautions required for the study of tautomerism discussed in the earlier edition [76AHCS1, pp. 14–20] are still valid.

V. Nonspectroscopic Physical Methods

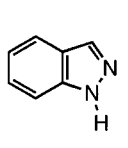
A. Basicity Measurements

This technique, when properly used, continues to be one of the most reliable to obtain quantitative data on tautomeric equilibria in solution.[3] Most papers use classic methods (spectrophotometric and potentiometric) to determine basic and acid ionization constants and then use these values and those of model compounds to calculate K_T. Examples concerning annular tautomerism of imidazoles (81PJC2525), of benzimidazoles [92MI(41)333], of histidine containing peptides [86MI(14)405], of azoles [87AHC(41)187], of 3(5)-nitropyrazole, and of the problems associated with compounds of very low basicity (97JPOC637) have been reported. Some examples concerning functional tautomerism are: (1) the study of 2-aminothiazoles [82JCS(P2)535], (2) the use of data obtained from UV spectroscopy (Section VII, C) to explain the microscopic pK_a values of 3-hydroxypyridine and pyridoxine [84JCS(P2)2047], (3) the site of protonation and tautomerism of cations derived from *C*-aminopyrazoles (85JHC997), (4) the tautomerism of 2-guanidinobenzimidazoles (87H1581),

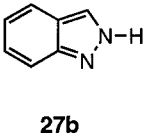
[3] Eq. (1–20) (76AHCS1, p. 22) must be written $S = (K_T + 1)K_T$.

and (5) the study of solvent effects on nicotinic and isonicotinic acid tautomerism (in water the zwitterions are more stable while in DMSO it is the neutral forms which are more stable) (96CJC613). The hydrogen-bonding acidity and basicity of NH-pyrazoles have been measured and, in some cases, related to annular tautomerism [87CR(305)567].

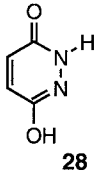
The results reported by Laynez on the use of calorimetric methods to obtain ionization and protonation enthalpies (88JA4105; 94JPC10606) deserve special mention. These methods have been used to ascertain the great predominance of 1*H*-indazole **27a** over 2*H*-indazole **27b** (94JPC10606) and discuss how *N*-methylation effects the basicity (88JA4105). This is important because *N*-methyl derivatives are often used as fixed derivatives (76AHCS1). P. J. Taylor is another author whose papers on the use of pK_a to study tautomerism must be considered as classic examples: the tautomerism of 1,2,3-triazole (**20**) and the role of lone-pair repulsions [89JCS(P2)1903]; the tautomerism of maleic hydrazide and the predominance of the oxo-hydroxy tautomer (**28**) (Section III,B) [93JCS(P2)331]; the tautomerism of pyrazolinones (93JA2352); and, especially, the paper on indazolinone **29** (where the proportion of the 2*H*-3-hydroxy tautomer **29c** was calculated to be $10^{-4.7}$), pyrazolinones, and the principle of vinylogy [96JCS(P2)2263] are particularly relevant.



27a



27b



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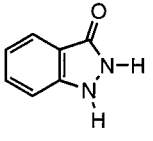
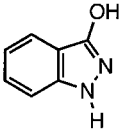
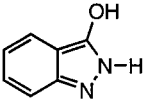


29a



29b



29c

B. Heats of Combustion and Reaction

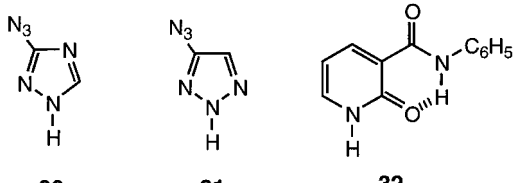
Work under this classification (76AHCS1, p. 31) continues to be sparse. Heat-of-solution data provide a useful method for estimating ΔH^0 for tautomeric processes in nonaqueous solvents, as was illustrated in the case of 2-pyridone **15a**/2-hydroxypyridine **15b** equilibrium (76TL2685). Heats of dehydration of 4-hydroxypyrazolines into pyrazoles and 5-hydroxyisoxazolines

into isoxazoles were used to estimate the aromaticity of these heterocycles, a property related to their tautomerism (Section IX) (78T1571). Enthalpies of solution in water and enthalpies of sublimation of 1-methyl-4-nitro- and 1-methyl-5-nitro-imidazoles were used to determine the tautomeric equilibrium of 4(5)-nitroimidazole in the gas phase (ΔG = 0.5 kcal mol^{-1}, the 4-nitro **18a** being slightly more stable than the 5-nitro tautomer **18b**) and in water (ΔG = 3 kcal mol^{-1}, the 4-nitro **18a** is much more stable) (89NJC151).

C. Dipole Moments

The use of dipole moments (dielectric constant method) shows a considerable decline from the time of our previous review (76AHCS1). The technique is time consuming and the progress in instrumentation has not been great. Moreover, the method is unsuitable when more than two tautomers are present. Although dipole moments are easily computed (see Section III,D), most theoreticians think that only gas-phase values (from MW spectroscopy, see Section VII,A) are useful to check the calculated values.

Continuing to use dipole moments to study tautomerism (78BSB189), Fayet has shown that from the dipole moment at two temperatures together with vectorial calculations both the preferred tautomer and the conformation of azido group for compounds **30** and **31** can be determined. This method demonstrated the predominance of 4-nitroimidazole over 5-nitroimidazole tautomer in dioxane (89NJC151) and the similar stabilities of both tautomers in the case of 3(5)-phenylpyrazoles (95BSB383). Fayet also studied the problem of 2-hydroxynicotinamides (**32**), where the limitations of the method are discussed [84BSF(II)233].



30 **31** **32**

Other authors have used dipole moments as an auxiliary technique to other physicochemical methods. Thus, Lumbroso has studied the tautomerism of 5-(*p*-aryl)tetrazoles in function of the substituent at the *para* position and compared the results with those obtained by ^{13}C NMR spectroscopy (Section VI,C) (80JHC1373). For a detailed description of Lumbroso's technique see [81JST(77)239].

D. Diffraction Methods

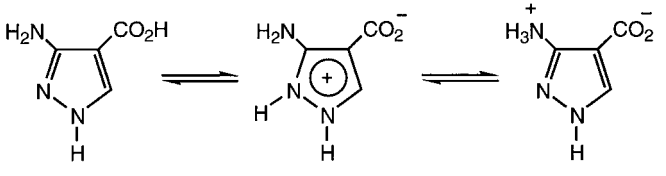
1. *Introduction*

A most notable change with regard to the previous edition is the extraordinary development of diffraction methods. In 1974 (the last year which was covered comprehensively in 76AHCS1) 16,266 structures (entries) were reported in the CSD [91MI(31)187]; today (April 1998 version) there are 177,681. Concerning tautomerism, two cases are to be considered. First, compounds for which other methods to study the solid state (for instance, IR and CPMAS NMR) yield clear-cut answers and which generally correspond to large differences in stability between tautomers (for instance, aminopyridines). Second, annular tautomerism of azoles where neither IR [not even CPMAS NMR (Section VI,F)] nor differences in stability permit easy determination of the tautomer present in the crystal. In this last situation diffraction methods are invaluable. Another case in which diffraction methods are also necessary is in the determination of equilibria between neutral and zwitterionic tautomers. Thus, in the case of 3-aminopyrazole-4-carboxylic acid **33a** (two annular tautomers) it has been established that this compound exists as the zwitterion **33b** (note that the proton is on the annular nitrogen atom and not on the amino group as in **33c**) (Scheme 13) [98AX(C)253].

2. *X-Ray Diffraction*

The X-ray studies of tautomeric compounds have demonstrated that several cases can be distinguished (Table VII) (94JHC695).

The first case is the most common by far. Thus, the annular tautomerism of nitroimidazoles (80CSC709), pyrazoles [92JCS(P2)1737; 96AX(B)746; 97JPOC637, 97T10783; 99AX(B)411; 99H227], and 1,2,4-triazole [97ZK(212)213] has been determined by X-ray crystallography. Other studies discussed the functional tautomerism of pyrazolones (see [97AQ(IE)219] for a review) where only NH and OH tautomers were found [85AJC401, 86BCJ121,



33a **33b** **33c**

Scheme 13

TABLE VII

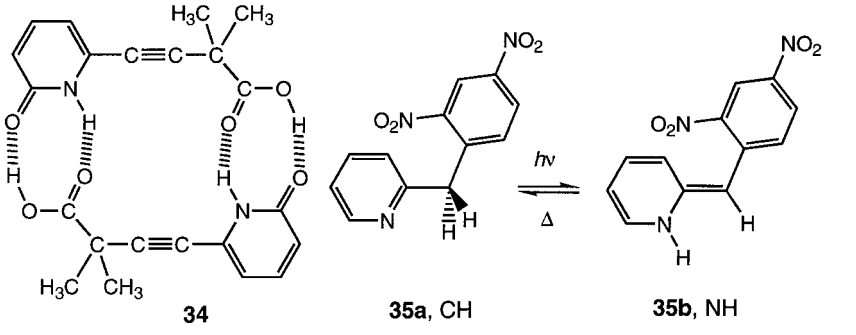
SOLID STATE AND TAUTOMERISM: DIFFRACTION METHODS

1. Only one tautomer is present in the crystal, no dynamic disorder
2. Only one tautomer is present in the crystal, but there is dynamic disorder (autotrope)
3. Two tautomers are present in the crystal, no dynamic disorder
4. Two tautomers are present in the crystal in equilibrium (dynamic disorder)
5. Two tautomers crystallize separately (desmotropy)
6. Tautomeric compounds as guest included in a host (static or dynamic)

95AX(C)1310, 97T5617, 98AX(C)136, 98JST(447)71] [for the only CH tautomer present in the solid state, see 98NJC1421, for indazolinones see 86JCS(P2)1677). Several papers reported the mesoionic structure of 5-imidazolinones (75TL4031; 89S641; 97JOC7037) and 1,2,3-triazole-5-thiones (93BSB1), while the classic structures for functional tautomers of different five-membered-ring derivatives were established [86MI(39)688; 87BAU303; 89H165; 95AJC1609; 97JCS(P2)721, 97JCS(P2)1783, 97JPC(B)3605], including 1-hydroxypyrazole, which exists as such (95LA1563), and Tinuvin P (92JPC10225) and perimidin-2-one [94HCA121].

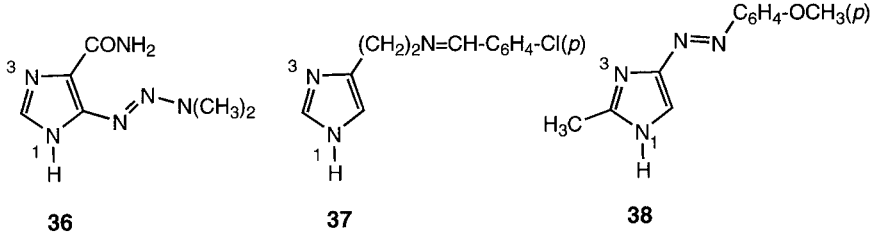
In the azine series, the oxo structure of the 2-pyridone/lauric acid complex [96MI(13)65], the thione structure of 4-thiopyridone (92JPOC191), the oxo-structure of pyridazinones (95AJC1601) and pyrazinones (97JHC773), the imino structure of nitraminopyridines (96ACSA808; 97T17211), and the structure of the cation of 9-aminoacridine [96MI(276)91] are classic examples of the utility of this technique. Less expected are Lippert's results on the rare tautomers of nucleobases induced by complexation with metals, the imino-oxo tautomer of cytosine (86JA6616; 98CEJ397), and the 2-oxo-4-hydroxo form of uracil (89JA7213), and those of Bertolasi and Gilli on intermolecular N-H···O hydrogen bonds (HBs) assisted by resonance, which include several heterocyclic compounds [95AX(B)1004; 98AX(B)50]. The HB network between carboxylic acids and 2-pyridone has been studied both in a symmetrical intermolecular case (cocrystal) [96MI(13)65] and in an unsymmetrical intramolecular one: formation of dimer **34** (97JA3802) (Scheme 14). A series of papers by Eichen (97JA7167 and references therein) describe an interesting case of photoinduced proton transfer which takes place in the crystalline state involving 2-(2,4-dinitrobenzyl)pyridine **35.** Both the CH and NH tautomers were characterized by X-ray crystallography. These compounds have second-order nonlinear optical properties [96CPL(258)485].

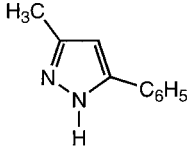
Examples of dynamic processes involving two, three, or four identical tautomers (degenerate or autotrope annular tautomerism) have been found in pyrazoles (type 2 of Table VII). Thus, 3,5-diphenyl-4-bromopyrazole and 3,5-di-*tert*-butylpyrazole (dimers), 3,5-dimethyl-pyrazole (trimer),



SCHEME 14

and 3,5-diphenylpyrazole (tetramer) all undergo proton transfer in the solid state (85JA5290; 89JA7304; 94JHC695; 95JOC1965). Examples of type 3 are relatively frequent in the case of annular tautomers of NH-azoles. Most examples involve 1*H*- and 3*H*-imidazoles such as the antitumor agent 5-(3,3-dimethyl-1-triazenyl)imidazole-4-carboxamide (NSC-45388) (**36**) [79AX(B)2051], *N*-(4-chlorobenzylidene)-2-(4-imidazolyl)ethylamine (**37**) [92AX(C)961], and 4(5)-(*p*-methoxyphenylazo)-2-methyl-imidazole (**38**) [96AX(C)2943]; but are also found in the case of NH-pyrazoles: 3(5)-methyl-5(3)-phenylpyrazole (95JHC451) (**39**) and 3(5)-amino-5(3)-(*p*-bromophenyl)pyrazole (**40**) (97T10783). Probably the most fascinating case of type 3 is 1,2,3-triazole **20,** studied by Goddard [97AX(C)1846]. This compound is the only parent azole liquid at room temperature (if one excludes pyrrole, also reported in the same paper); the reason becomes apparent when the structure was determined at low temperature (the crystallization occurs in a Lindemann glass capillary in the diffractometer). The two tautomers, 1*H* (**20b**) and 2*H* (**20a**), were present, forming chains of HBs (the compound shows proton disorder involving the 1 and 3 positions of **20b**). Compound (**39**) (95JHC451) crystallizes into two polymorphs, both tetramers, and one of them presents proton transfer in the solid state (type 4 of Table VII). Another example of type 4 is provided by 5-methyl-4,5,6,7-tetrahydro-1*H*-indazole **4** (97CEJ121).





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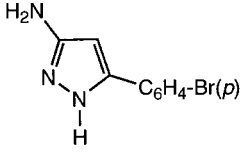

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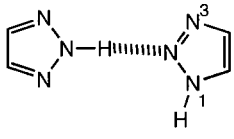
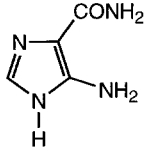
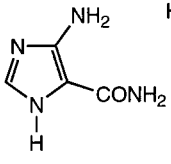


20a **20b**

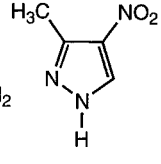
Desmotropy (type 5 of Table VII) is less frequent; one example is AICA **41** [4(5)-amino-1(3)*H*-imidazole-5(4)-carboxamide], which, when crystallized with *iso*-propanol, is in the form 1*H* (**41a**·*i*PrOH) and when crystallized with water is in the 3*H*-tautomeric form (**41b**·H_2O) [80AX(B)2323]. Another example is 3(5)-methyl-4-nitropyrazole, where both tautomers, **42a** and **42b,** can be isolated depending on the crystallization solvent [94JCS(CC)1143]. Two tautomers of 1-phenyl-3-methyl-4-benzoylpyrazolin-5-one (**43**) can be obtained separately and their structures have been determined: the OH **43a** (with an intramolecular HB) [95AX(C)1310] and the NH **43b** with intermolecular HBs [85AJC401; 95AX(C)1310]. In the case of the related isoxazolinone **44** only the NH tautomer has been found [95ZN(B)37].



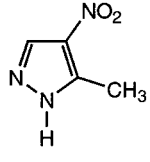
41a



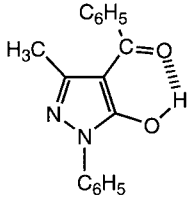
41b



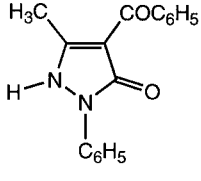
42a



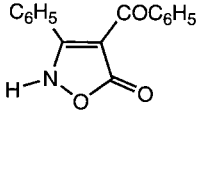
42b



43a



43b



44

Tautomerism involving compounds included in a host molecule (type 6) has been studied, in some cases involving triazoles and pyrazoles [87CL2317; 88CL1061; 93JCS(CC)1139] [the last reference describes a case of proton transfer for pyrazole included in 1,1-di(2,4-dimethylphenyl)but-2-yn-1-ol],

and it was concluded that the tautomer present in the crystal usually corresponds to the most abundant one in solution [97T10783]. However, dangers in this generalization have been pointed out [97AX(C)1846]. When the difference in stability between two tautomers is small, both have similar probabilities to crystallize. In some rare cases, both crystallize separately (polymorphism and desmotropy), but in most cases, only one of them is found in the solid state. The present level of our knowledge of crystal packing calculations cannot predict which would crystallize in any such case.

3. *Neutron Diffraction*

Some structures have been solved by neutron diffraction, though this technique is relatively unimportant for tautomerism. The main advantage of neutron over X-ray diffraction is that the H atoms (including the tautomeric one) are more accurately located. However, in practice X-ray structure determinations usually unambiguously determine which tautomer is present. The position of the tautomeric proton can be inferred from the distances and angles involving the heavy atoms close to it. To illustrate the use of neutron diffraction we quote two examples: 4-hydroxy-2-pyridone [94MI(24)371] and 2,6-diaminopyridine [87AX(C)2191].

4. *Electron Diffraction*

No example of the use of electron diffraction (ED) to study the prototropic tautomerism of a heteroaromatic compound was available at the time of our first revision [76AHCS1]. The situation has not much changed probably because electron diffraction, although requiring much less expensive instrumentation than microwave spectroscopy (MW, see Section VII,A), gives less information about the structure of molecules in the gas phase. The fact that 1,2,3-triazole **20** exists in the gas phase mainly as 2*H*-tautomer, **20a,** was established by MW and its geometry determined by ED [88ACSA(A)500]. The structures (*C*s) of 3,5-dimethylpyrazole and of 3,5-bis(trifluoromethyl)pyrazole have been determined by ED and the tautomeric NH proton localized [93JST(291)211].

VI. Nuclear Magnetic Resonance

A. Introduction

This technique continues to be that preferred by organic chemists to study tautomerism. Some reviews relevant for tautomerism have appeared:

"^{15}N NMR Spectroscopy—Applications in Heterocyclic Chemistry" (84BSB559); "Nitrogen NMR and Molecular Interactions" [85PIA(94)241]; "^{15}N NMR Spectroscopy—New Methods and Applications" [86AG (E)383]; "Tautomerism in View of ^{1}H, ^{13}C, ^{14}N and ^{15}N NMR" (88WCH 133); "High-Resolution Solid-State NMR Study of Reversible 1,5-Proton Shifts in Organic Solids" [90MRC(S)29]; "^{13}C NMR of Pyrazoles" (93MRC107); "Proton Transfer in Solid Heterocycles: an X-Ray and CPMAS NMR Study" (94JHC695); "Hydrogen Bonding and Tautomerism Studied by Isotope Effects on Chemical Shifts" [94JST(321)79]; "^{13}C NMR of Indazoles" (95CHE1006); "Nuclear Magnetic Resonance of Nitroazoles" [96MI(1)187]; "NMR Study of C- and N-Trimethylsilylazole Derivatives" (98MRC110); "Isotope Effects on Chemical Shifts as a Tool in Structural Studies" (96MI1); and "Substituent Effects on the ^{15}N NMR Parameters of Azoles" (97MRC35).

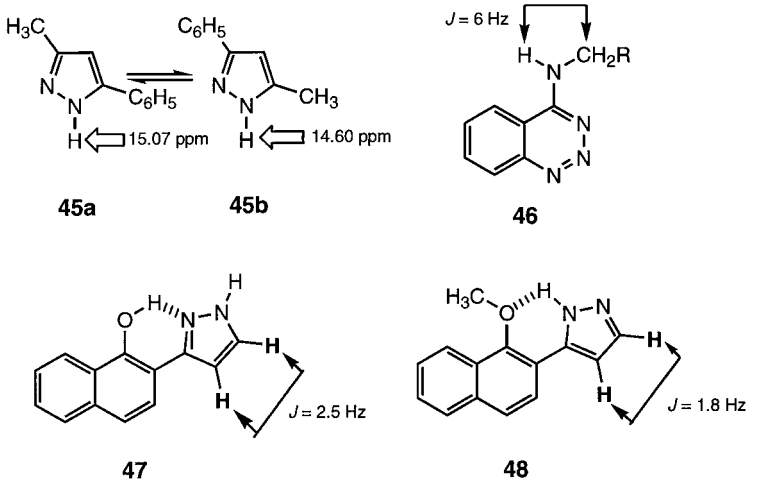
B. Proton Nuclear Magnetic Resonance

^{1}H^{-15}N coupling constants, often measured in ^{1}H NMR using labeled compounds, are discussed together with ^{15}N NMR (Section VI,D). Taking into account that ^{1}H NMR data are now present in every paper dealing explicitly or implicitly with tautomerism, only a few articles are documented in this section.

The study of tautomerism using ^{1}H NMR spectroscopy is simple when the tautomers give separate signals (84B2906); otherwise, interpolation methods need to be applied, which entail several sources of imprecision [83JPR(325)238]. A paper reports the observation of two NH signals for the ^{15}N-labeled tautomers of 3(5)-methyl-5(3)-phenylpyrazole (**45**) in toluene-d_8 at 190 K (Scheme 15) [92JCS(P2)1737].

Alongside the chemical shifts, ^{1}H-^{1}H coupling constants are useful to determine the major tautomeric structure and sometimes even the tautomeric equilibrium constant. This technique has been applied to the 2-pyridone/2-hydroxypyridine equilibrium [83THE(94)163] and to the substituted 4-amino-1,2,3-benzotriazines (**46**), where the observation in DMSO-d_6 of a ^{3}J coupling between the CH_2 and the NH was used as an argument for the existence of the amino tautomer in solution [84JCR(S)62]. In tautomeric NH-pyrazoles, the determination of a $^{3}J = 2.5$ Hz for **47** and 1.8 Hz for **48** was used as evidence for their different tautomeric structures (95JOC3427). Sternhell *et al.* (92JHC935) discussed in detail the utility of ^{4}J(Me-C=C−CH) coupling constants in structural chemistry including several examples of heterocyclic tautomerism.

Further examples of the application of ^{1}H NMR spectroscopy include



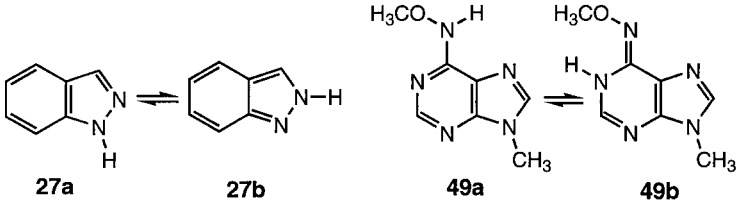
SCHEME 15

(1) the use of NOE spectroscopy in the case of pyridazines (95AJC1601); (2) the determination of the ΔG of association in HB dimers: 2-aminopyridine dimer and 2-aminopyridine/2-pyridone complex [84SA(A)623] and the dimer formed by a 2,2-dimethyl-3-butynoic acid with a pyridone terminus (see Section V,D,2) (97JA3802); and (3) tautomerism in supramolecular assemblies: the case of the inclusion complexes between pyridoxine and β- and γ-cyclodextrins [96MI(25)113].

C. Carbon-13 Nuclear Magnetic Resonance

^{13}C-^{15}N coupling constants often measured in ^{13}C NMR using labeled compounds are discussed together with ^{15}N NMR (Section VI,D). ^{13}C NMR today is just as routine as is ^{1}H NMR spectroscopy and this results in a huge number of publications where ^{13}C NMR and tautomerism figure together. We first discuss some cases where ^{13}C chemical shifts have been used to ascertain the position of the equilibrium.

There was never any doubt that the major tautomer in the case of indazole **27** is the 1*H*-one **27a** (Scheme 16), and ^{13}C chemical shifts compared with those of the two *N*-methyl derivatives confirmed that this is the case in DMSO-d_6 (77OMR716). ^{13}C NMR has been used to determine the equilibrium isomeric composition of N-CHROH, N-$C(CH_3)_2OH$, N-$COCH_3$ and N-$Si(CH_3)_3$ derivatives for azoles and benzazoles, the conclusion being that this composition parallels the annular tautomeric composition [78JCS(P2)99]. The tautomerism of 1-hydroxybenzotriazole was also studied



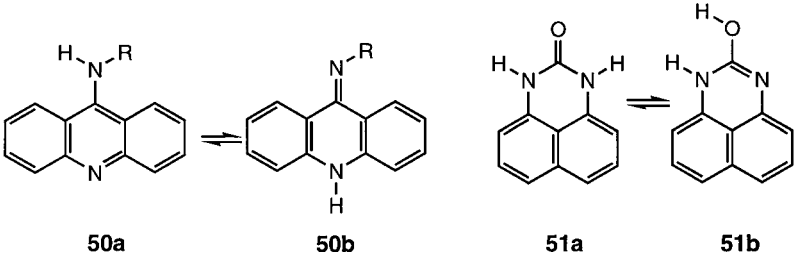
SCHEME 16

with ^{13}C NMR spectroscopy (80OMR339). In a review (93MRC107) the use of ^{13}C NMR spectroscopy for studying the annular tautomerism of pyrazoles is discussed.

In solution, XH/Y ⇌ X/HY tautomerism almost always yields average signals for XH and HY tautomers when X and Y are heteroatoms. However, there are some reports of the observation of both tautomers in ^{13}C NMR spectroscopy, for instance in N^6-methoxyadenosine **49a** and **49b** [84B2906]. The broadening of some ^{13}C signals in 9-alkylaminoacridines (**50**) has been explained by a slow equilibrium between the amino **50a** and imino **50b** tautomers (for R = H, only **50a** was present and no broadening was observed) [88MI(21)809]. It has been reported that both for perimidin-2-one (**51a**) and perimidin-2-ol (**51b**) narrow signals were observed in DMSO-d_6 (88MRC191) but this result has not been reproduced (only **51a** was found) and is much in doubt (Scheme 17) (94HCA121).

At low temperatures (see Section VI,G) the ^{13}C signals corresponding to different tautomers can frequently be observed, for instance, in some NH-pyrazoles [91G477; 92JCS(P2)1737; 98MRC110]. In the case of 2-heteroarylbenzoxazoles (89JHC387) and 2-aryl-(96JHC1711) and 2-heteroaryl- [89JHC387; 92MI(41)223; 96JHC1711] benzimidazoles and their quaternary salts (89JHC387), the slow annular prototropy has been related to homodimers.

If only time-averaged signals are observed, it is necessary to resort to in-



SCHEME 17

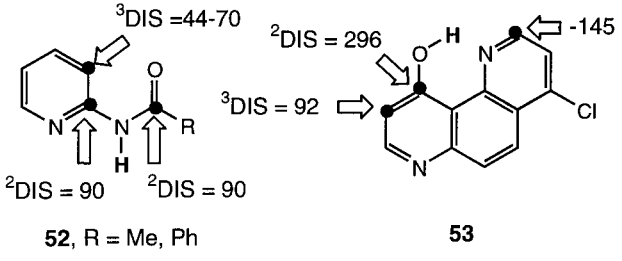
terpolation methods. The difficulty with interpolation is to estimate the differences in chemical shifts between the tautomer and the model compound (or fixed derivative), generally XMe and MeY (76AHCS1, p. 41). This problem has been discussed in a series of papers: for 2-XH benzothiazoles (X = O, S, NH, NR) (78OMR617), 3(5)-aminopyrazoles (79OMR587), benzimidazoles (82OMR188), pyrazolin-5-ones [83JPR(325)238], 5-aryltetrazoles [84JCS(P2)721], 3-methylthioimidazo[4,5-*e*]-*as*-triazine [86JCS(P2)931], studies of annular tautomerism of azoles and functional tautomerism of azoles and azines [87BAP305], and pH dependence of the ^{13}C chemical shifts of formycin [94MI(13)481].

Two alternatives to this classic approach have appeared recently. The first consists in using the experimental values obtained in the solid state by ^{13}C-CPMAS NMR (see Section VI,F) for the tautomer present in the crystal (93CJC678; 94NJC269). In the very infrequent cases where both tautomers are present in the crystal (see Section V,D,2), both shifts can be used [97T10783]. The second approach consists of using theoretically calculated ^{13}C nuclear shieldings for each tautomer (see Section III,F). This has been done for benzotriazoles and 9-aminoacridine using the GIAO method [94JST(327)321; 97JPC(A)283].

^{1}H-^{13}C and ^{13}C-^{13}C coupling constants can be used as tools for determining K_T. This has been used in the case of purine (82JA4167), 2-XH pyrazines (X = O, S, NH) (82TL4785), for determining the protonation site of *C*-aminopyrazoles (85MRC367), and in the case of 3-methylthioimidazo[4,5-*e*]-*as*-triazine [86JCS(P2)931]. A convincing argument for the use of coupling constants (including ^{13}C-^{19}F couplings) in studies of tautomerism has been made by Begtrup (87MI371). Begtrup comments that, in order to be suitable, an NMR parameter should (1) not be influenced by the substituent used to fix the structure and (2) be sufficiently sensitive to tautomeric structure.

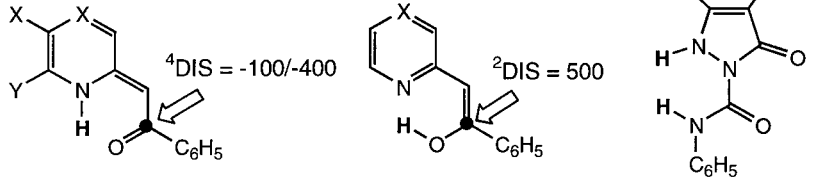
A novel application of NMR studies to tautomerism is based on DIS (Deuterium Induced Shifts), until now applied only to ^{13}C NMR chemical shifts [94JST(321)79; 95JCS(P2)1901; 96MI1; 98JA9063]. The method consists of measuring secondary isotope effects on chemical shifts, i.e., changes in chemical shifts on one nucleus, typically ^{13}C, with the change of isotope from ^{1}H to ^{2}H (D) at another position. A positive DIS denotes shielding, $DIS = \delta_C(H) - \delta_C(D)$; because DIS values are very small it is preferable to use ppb (parts per billion) instead of ppm. The effect observed on carbons at various distances enables the position of the tautomeric proton to be inferred and hence the predominant tautomer to be deduced. Moreover, the easiest proton to exchange by deuterium (often only partially, allowing simultaneous observation of the ^{13}C signal with and without DIS) is precisely the tautomeric proton. The technique has been used systematically by

I. Ghiviriga and one of the authors of this chapter [95JCS(P2)1651; 96MRC518; 97JCS(P2)2605, 97T5617].



52, R = Me, Ph

53



54

X = N, CH

55

56

X = O, S

Note: for **52-56**, the units for ^{n}DIS are ppb

In 2-acylaminopyridines (**52**), positive ^{2}DIS (two-bonds) effects are only consistent with an "amino" tautomer [95JCS(P2)1651]. The use of this methodology is discussed in detail in the paper reporting DIS effects on 4-chloro-1,7-phenanthrolin-10-ol (**53**) where the relationship between DIS and the strength of the HB is examined (96MRC518). Enaminone **54** and enol **55** tautomers were identified through DIS effects (note the large and variable negative ^{4}DIS values in **54**) [97JCS(P2)2605]. Finally, the more complex situation of pyrazolinones **56** (two exchangeable NH protons) is discussed in the most recent paper (97T5617).

D. Nitrogen-15 Nuclear Magnetic Resonance

Organic chemistry is based on carbon, but nitrogen is fundamental to heterocyclic chemistry. Although there are many important aromatic heterocycles without nitrogen atoms (thiophene, furan, pyrylium salts, etc.), it is clear that the majority of heterocyclic systems contain nitrogen atoms. Thus, ^{15}N NMR spectroscopy (^{14}N NMR yields the same chemical shifts

and is not discussed) should be a method of choice for studying heterocyclic tautomerism. Until around 1980, the difficulties associated with ^{15}N NMR spectroscopy (low abundance, negative NOE) prevented its full exploration. The situation is different now and ^{15}N NMR spectroscopy without isotopic enrichment is routine although it has to be pointed out that most ^{15}N NMR studies concern the use of averaged signals. Observation of individual tautomers usually requires low-temperature spectra with broad ^{15}N NMR signals which, in turn, requires ^{15}N-labeled compounds. Until now, ^{15}N spectroscopy has neither revolutionized nor superseded more classic spectroscopies for the study of tautomerism, for reasons which are not discussed.

Interpolation methods based on ^{15}N chemical shifts require the use of the general equations. Those reported in the previous edition (76AHCS1, p. 29, see also 82JOC5132) have been slightly modified for the present purpose. We call P_X the observed average property, P_A and P_B the property of the individual tautomers (A or B), P_{MA} and P_{MB} a corresponding property that can be *measured* (in a model compound or in the solid state) or *calculated* theoretically, and P^*_A and P^*_B the correction factors defined as $P^* = P_M - P_A$. If the properties of individual tautomers could be measured, then $K_T = (P_X - P_B)/(P_A - P_X)$, otherwise $K_T = (P_X - P_{MB} - P^*_B)/(P_{MA} - P^*_A - P_X)$. In some instances, it is assumed that $P^*_A = P^*_B$, but this is not necessarily true. The quality of the interpolation depends on the ratio $(P_{MB} - P_{MA})/(P^*)$. In the case of ^{15}N chemical shifts (spectral range ~900 ppm), $P_{MB} - P_{MA}$ is larger than in the case of ^1H (spectral range ~12 ppm) or even ^{13}C chemical shifts (spectral range ~230 ppm). However, the same variation in range occurs for P^* and it is by no means evident that the ratio is more favorable in the case of ^{15}N NMR.

^{15}N NMR spectroscopy is dominated by the authors whose main contributions are reported in Table VIII. Witanowski, Stefaniak, and Webb are clearly the most relevant contributors to the use of ^{15}N NMR spectroscopy for the study of tautomerism. Limbach made a seminal contribution concerning the solid state and the mechanism of proton transfer. Recently, Kleinpeter has published several interesting papers in an ongoing series. Some reviews pertaining to ^{15}N NMR investigations of tautomerism have been published [81ZC47; 84BSB559; 85PIA(94)241; 87BAP305; 88WCH133; 94JHC695; 96MI(1)187; 97MRC35].

Papers describing the use of ^{15}N chemical shifts for the study of tautomerism, classified according to the type of tautomerism, are summarized in Table IX.

To illustrate the results summarized in Table IX, some examples are discussed in detail. The large number of papers discussing the annular tautomerism of azoles (first column) is exemplified by the studies concerning benzotriazole (**57**). Wofford, Forkey, and Russell, using pyrazoles and imi-

TABLE VIII

^{15}NMR SPECTROSCOPY: MAIN AUTHORS CONTRIBUTION

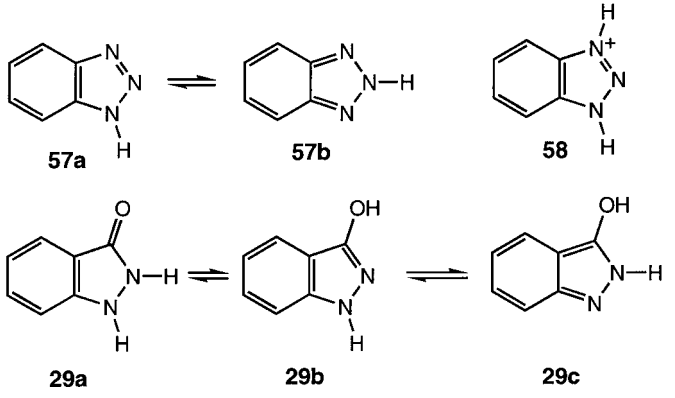
J. D. Roberts	M. Witanowski, L. Stefaniak, and G. A. Webb		H. H. Limbach	E. Kleinpeter
82JA3162	78OMR27;	81PJC1441;	89JA7304	95JST(355)273
82JA3945	85BAP375,	85BAP437,	92JA9657	97JST(435)65
83JA2050	85MI(4)103,	85MRC166,	92JCS(P2)1737	97MI(3)375
	85MRC181,	85MRC784,	93JCS(CC)1139	97THE(401)1
	85PIA(94)241;	86BAP289,	94JHC695	
	86BCJ3263,	86JST(140)311,	94JPC8752	
	86MRC911;	87BAP81,	94MRC699	
	87BAP85,	87BAP305,	95JHC451	
	87MRC721;	88WCH133;	95JOC1965	
	91BAP317;	94JST(327)321;	95MI(4)121	
	95BAP287,	95MI(4)121;	96JMR(120A)46	
	96MRC453;	97MRC237	97BBPG889	
			97JCS(P2)1867	

dazoles (where $K_T = 1$) to estimate P^* (N-methylation), reached the conclusion that the mole fraction of **57b** is 0.02 ± 0.02 in $CDCl_3$ and 0.02 ± 0.05 in DMSO-d_6 (82JOC5132). According to Schilf, Stefaniak, Witanowski, and Webb (85BAP437), these fractions are 0.05 ± 0.05 in $CDCl_3$, 0.05 ± 0.05 in acetone-d_6, 0.09 ± 0.05 in DMSO-d_6 and 0.06 ± 0.05 in methanol-d_4. Stefaniak and Webb also determined that protonation of **57a** occurs at N-3 in trifluoroacetic acid, forming the cation **58** (Scheme 18) [94JST(327)321].

TABLE IX

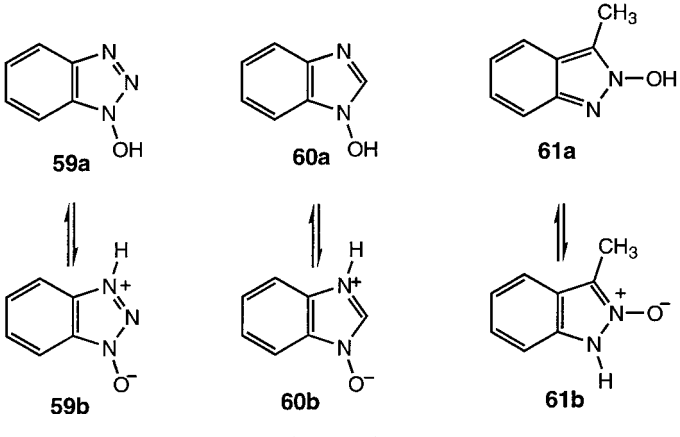
^{15}N NMR SPECTROSCOPY: USE OF δ^{15}N CHEMICAL SHIFTS

Azoles annular neutral and cations	Azoles functional C-X (X = OH, SH, NHR)	Azoles functional N-OH	Azines annular cations	Azines functional
78OMR27; 82JOC5132,	85BAP375	85MRC181	83CB2001	81PJC1441
82JA3162, 82JA3945,	85MI(4)103	86JST(140)311		82TL4785
82OMR10; 83JA2050;	85MRC166	87MRC721		95JST(355)273
84BSB559; 85BAP375,	85MRC784			97JST(435)65
85BAP437, 85MRC166;	86BCJ3263			97MI(3)375
86BAP289, 86BCJ3263,	86JCS(P2)1677			97THE(401)1
86JCS(P2)931, 86MRC911;	86MRC911			
87BAP85; 89MRC1;	87BAP81			
92JCS(P2)1737; 93JA6813;	91BAP317			
94JST(327)327, 94NJC269;	93JCS(P2)1597			
95BAP287; 97MRC237,				
97T10783; 98MRC343				



SCHEME 18

Two papers, which appeared almost simultaneously, examined the tautomerism of indazolinone (**29**) in DMSO (second column of Table IX) and concluded that the mole fractions are 0.75 ± 0.03 of **29b** and 0.25 ± 0.03 of **29a** (85MRC784) or 0.85 of **29b** and 0.15 of **29a** [86JCS(P2)1677], which show both the general agreement and the errors involved in interpolation methods (tautomer **29c** is not present in detectable amounts). The method has also been applied by Stefaniak and Webb to the *N*-hydroxy/*N*-oxide tautomerism of benzotriazole **59** (85MRC181), benzimidazole **60** [86JST(140)311], and 2-hydroxy-3-methyl-indazole **61** (87MRC721) derivatives (third column of Table IX). In all cases, both tautomers are present in amounts dependent on the solvent used (Scheme 19).



SCHEME 19

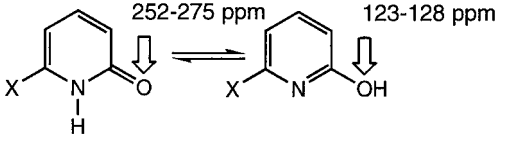
The examples in the fourth column (Table IX) concern the protonation of purine and adenine and their derivatives while those of the last column mainly reflect Kleinpeter's contributions (Table VIII) to the functional tautomerism of 7-hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidines.

Other authors have used ^{15}N coupling constants instead of (or simultaneously with) ^{15}N chemical shifts. In some cases they have been determined by ^{15}N NMR spectroscopy, in other cases, labeled compounds and ^{1}H or ^{13}C NMR spectroscopies have provided these couplings. These couplings have been used for determining tautomeric composition (see the discussion by Begtrup in 87MI371). Most examples involved ^{1}H-^{15}N and ^{13}C-^{15}N [79JOC1627; 80JA2881; 83JPR(325)238; 87MI371; 96MRC453] but some examples of ^{15}N-^{15}N couplings are also available [87MI371; 89JPR(331)11]. The difficult problem of determining the relative amount of NH and OH tautomers in pyrazolin-5-ones has been solved using the value of ^{13}C-^{15}N coupling constants [83JPR(325)238].

Finally, solid-state studies (see Section VI,F) (for a pioneering paper see [82JA1192]) have been carried out by Limbach (Table VIII) and generally involve a DNMR (see Section VI,G). Three of the most interesting contributions, all based on 3,5-dimethylpyrazole dynamic properties, are devoted to the exploration of alumina and silica cavities (94JPC8752), the determination of ^{15}N chemical shift tensors and HB geometries [96JMR(120A)46], and the study of kinetic H/D isotope and tunnel effects (97BBPG889).

E. Other Nuclei Nuclear Magnetic Resonance

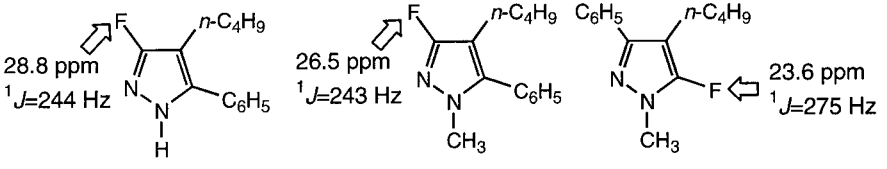
A most promising nucleus for studying tautomerism is ^{17}O, since large differences between C=O and C-OH signals are to be expected. Just as is the case for ^{15}N NMR spectroscopy (see Section VI,D), ^{17}O chemical shifts are very sensitive to effects other than tautomerism itself. Nevertheless, Facelli *et al.* [92JPC7895] have applied ^{17}O-NMR to the study of 6-X-2-pyridone **62** tautomerism (Scheme 20). Using pyridine-d_5 as solvent and LORG calculations (see Section III,F), they estimated that for X = H or CH_3, the oxo tautomer **62a** predominates, while for X = Cl or NH_2, the major isomer is hydroxy tautomer **62b.** Using their data (reference external water), it is possible to determine the populations of both tautomers by interpolation (Section III,B): X = H (2% OH), X = Cl (100% OH), X = NH_2 (33% OH), and X = CH_3 (<1% OH). It can be predicted that ^{17}O spectroscopy will be used for other studies based on comparisons of solvents, model compounds, and temperature effects. Oxygen-17 NMR has also been used to establish the phenolic structure of 4-azido-6-(2′-hydroxyphenyl)pyrimidines [95MI(44)1435].



62a **62b**

SCHEME 20

Fluorine-19 NMR has also been used to study annular tautomerism in pyrazoles, both for fluoro- and for trifluoromethyl-pyrazoles (99H355). Comparison of data [^{19}F chemical shifts and ^{1}J (^{13}C-^{19}F) coupling constants of **64a** and **64b**] shows that compound **63** is a 3-fluoro tautomer (96JOC2763). Examples of application to trifluoromethylpyrazoles can be found in a review (95OPP33).



63 **64a** **64b**

The possible use of ^{29}Si NMR for the study of the prototropy and silylotropy of pyrazoles has been explored (98MRC110). Another paper reports the use of ^{31}P NMR for establishing that 3-phenyl-4-benzoylisoxazol-5-one is hydrogen-bonded to tri-*n*-octylphosphine as the NH-tautomer [96MI(14)653].

F. SOLID-STATE NUCLEAR MAGNETIC RESONANCE

This technique, which is predicted to develop considerably in the coming years (for instance, incorporating ^{1}H NMR studies), is an excellent complement to X-ray crystallography (Section V,D,2) for two reasons: (1) it is not necessary to obtain single crystals and (2) dynamic phenomena can easily be distinguished from static disorder through DNMR experiments (Section VI,G). The most frequently used techniques are MAS (Magic Angle Spinning) and CPMAS (Cross Polarization MAS).

Some reviews relevant for this section concern ^{15}N CPMAS [86AG(E)383] of pyrazoles, including ^{13}C CPMAS results (93MRC107) and proton transfer in solid heterocycles (94JHC695). The most relevant studies reported in Table X are (1) the use of ^{13}C CPMAS NMR to identify

TABLE X

SOLID STATE TAUTOMERISM: NMR (MAS AND CPMAS)

^{13}C NMR		^{15}N NMR	
Static	Dynamic	Static	Dynamic
	Annular		
Imidazoles: 81JCS(CC)1207; 87H333; 90CPB3140	Pyrazoles: 85JA5290; 97JCS(P2)721	Imidazoles: 82JA1192	Pyrazoles: 89JA7304; 92JA9657; 93JCS(CC)1139; 94JPC8752; 95JHC451, 95JOC1965; 97BBPG889, 97JCS(P2)1867
Pyrazoles: 81JCS(CC)1207; 88CJC1141; 93CJC678; 94JCS(CC)1143; 97T10783	Porphyrins: 90MRC(S)29	Histidine: 82JA1192	
1,2,4-Triazoles: 83H1713		Carnosine: 90CPB3140	
Tetrazoles: 83H1713; 95MI(4)121		Pyrazoles: 94MRC699; 96JMR(120A)46	
Benzimidazoles: 83H1713; 92MI(41)233		Tetrazoles: 95MI(4)121	Tetrazoles: 98JCS(P2)475
Indazoles: 83H1713; 93CJC678		Benzotriazoles: 94JST(327)321	Porphyrins: 86AG(E)383; 96JA11101
Benzotriazoles: 83H1713; 94JST(327)321			
	Functional		
Pyrazolidones: 87H333; 93BSB735; 97AQ(IE)219; 98JST(447)71		Pyridone, pyrimidone, uracil, cytosine [00MIip].	
Rubazoic acids: 93JCS(P2)1597			
Indazolinone: 86JCS(P2)1677			
Benzoxazolin-2-thione: 83H1713			
Pyridone, pyrimidone: 00MIip			

the presence of two tautomers in the same unit cell (Section V,D,2) (87H333, 97T10783); (2) the use of ^{13}C CPMAS NMR to characterize two tautomers crystallizing into two different crystals (desmotropy, Section V,D,2) [94JCS(CC)1143]; (3) the use of ^{15}N-^{2}H double-labeled compounds for the determination of geometric parameters in hydrogen-bonded pyrazoles [96JMR(120A)46]; (4) those of Frydman and Olivieri concerning ^{13}C CPMAS dynamic studies of porphyrins [90MRC(S)29] and those of Limbach concerning ^{15}N CPMAS dynamic studies of the same compounds (96JA11101); (5) the study of the dynamic behavior of a pyrazole in a guest cavity [93JCS(CC)1139]; (6) the use of the dynamic properties of 3,5-dimethylpyrazole (a cyclic trimer in the solid state) to explore the surface properties of silica and alumina (94JPC8752); (7) the study of dynamic properties of pyrazoles whose X-ray structures cannot be determined (95JHC451); and (8) the combined use of ^{15}N CPMAS NMR and X-ray crystallography to determine the dynamic behavior of a 5-aryl-2*H*-tetrazole derivative [98JCS(P2)475].

G. Temperature Coalescence Studies (DNMR)

It must be emphasized that all time-dependent chemical phenomena, such as tautomerism, are sensitive to temperature changes. In this section, we treat classic DNMR (dynamic NMR) studies and cases of changes in the NMR spectra with temperature together. In Table XI we have classified these studies according to the physical state of the sample and to the nuclei

TABLE XI
Dynamic NMR Studies in Solution and in the Solid State

Solution		Solid state	
^{1}H and ^{13}C NMR	^{15}N NMR	^{13}C NMR	^{15}N NMR
75TL4085	92JCS(P2)1737	85JA5290	89JA7304
77H911	94MRC699	89JA7304	92JA9657
79AQ701		93JCS(CC)1139	93JCS(CC)1139
84JCS(P2)1025			94JPC8752
92MI(41)233			95JHC451
92JCS(P2)1737			95JOC1965
93CJC1443			97BBPG889
94NJC269			97JCS(P2)1867
97JCS(P2)721			98JCS(P2)475
98MRC110			
98JPOC411			

TABLE XII
DYNAMIC NMR STUDIES ACCORDING TO THE TAUTOMERISM INVOLVED

Both tautomers at RT (unusual)	Both tautomers on cooling (K_T)	Annular tautomerism in azoles (ΔG and $\Delta G^{\ddagger}$)
75TL4085 77H911 92MI(41)233 94JOC639 95T13365	92JCS(P2)1737 94NJC269 98MRC110	75TL4085; 79AQ701; 84JCS(P2)1025; 85JA5290; 89JA7304; 92JA9657; 93CJC1443, 93JCS(CC)1139; 94JPC8752, 94MRC699; 95JHC451, 95JOC1965; 97BBPG889, 97JCS(P2)721, 97JCS(P2)1867; 98JCS(P2)475, 98MRC110, 98JPOC411

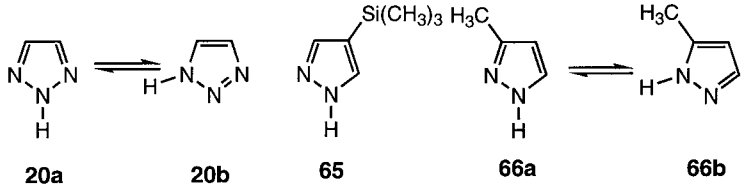
(remember that ^{1}H NMR spectra are difficult to obtain in the solid state). Table XII is an attempt to classify the same references with regard to the structural information obtained.

The imbalance between ^{13}C and ^{15}N NMR studies in the solid state (Section VI,F) partly reflects the fact that it is easier to introduce ^{15}N than ^{13}C into heterocyclic compounds, particularly azoles (DNMR in the solid state usually requires isotopic enrichment). Compared to solution studies, solid-state intermolecular proton transfer between tautomers has the enormous advantage that the structure of the species involved is precisely defined.

Papers in the first column of Table XII report the fact that some NH-benzimidazoles show slow annular tautomerism at room temperature, leading to the splitting of ^{1}H and ^{13}C NMR signals. This observation, unusual at the time of the first reports (75TL4085; 77H911), has become more common in recent times [92MI(41)223; 95T13365]. Since activation barriers for *intermolecular* proton shifts are very dependent on the concentration (the tendency is to work with more diluted solutions), the nature and purity of the solvent, the field strength, and the temperature, it is to be expected that the observation of individual tautomers, when previously only average signals were reported, will occur more often as conditions are more finely tuned. Two independent authors report that the signals corresponding to the CH and NH/OH tautomers of pyrazolinones become broad at >100°C (1-phenyl-3-acetylaminopyrazolin-5-one) (74BSF291) and at 95°C (1-phenyl-3-methylpyrazolin-5-one) [83JPR(325)238], but the activation barrier of the (probably intermolecular) proton transfer was not given.

Some papers (second column of Table XII) report the observation of individual tautomers on cooling. These results were used to determine the populations by integration and, therefore, of K_T and ΔG.

The largest series of papers (third column) is related to the study of annular tautomerism in azoles. This class of tautomerism is especially well suited for DNMR because in many cases $K_T = 1$ (autotrope) and because the activation barriers are in the range easy to be measured by NMR. To

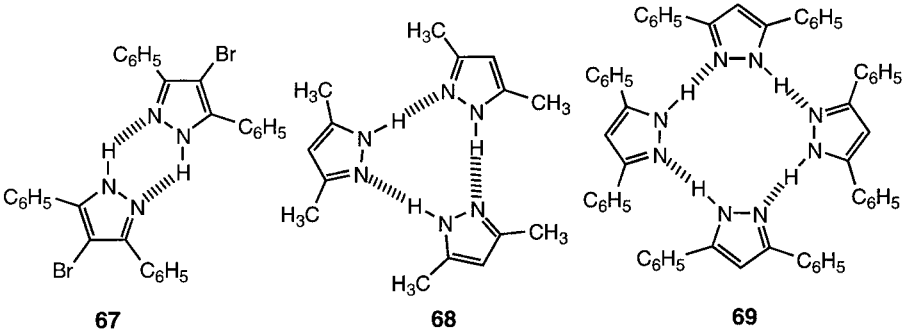


SCHEME 21

illustrate these contributions, we have selected papers by Lunazzi [84JCS(P2)1025] concerning the tautomerism of triazoles and by Larina (98MRC110) describing some simple pyrazoles, both in solution. For solid-state studies, we discuss two papers by Limbach (92JA9657; 97BBPG889) concerning the solid-state tautomerism of pyrazoles.

Lunazzi *et al.* [84JCS(P2)1025] reported the first reliable data on the behavior of 1,2,3-triazole **20** in solution (Scheme 21). Using ^{1}H NMR at 300 MHz and lowering the temperature to −98°C they determined not only the equilibrium constant but all the thermodynamic and kinetic parameters: ΔG^0_{273} = 0.55 kcal mol^{-1} (CD_2Cl_2) and 1.60 kcal mol^{-1} (toluene-d_8), ΔH, ΔS, $\Delta G\ddagger_{273}$ = 11.7 kcal mol^{-1} (CD_2Cl_2), $\Delta H\ddagger$ and $\Delta S\ddagger$. Larina *et al.* (98MRC110) used ^{1}H DNMR to determine the activation barrier of 4-trimethylsilylpyrazole (**65**) ($\Delta G\ddagger_C$ = 11.9 kcal mol^{-1}) and ^{13}C DNMR to determine the activation barrier of 3(5)-methylpyrazole (**66**) (54% **66a** − 46% **66b,** $\Delta G\ddagger_C$ = 10 kcal mol^{-1}) [similar barriers have been reported for other pyrazoles (93CJC1443)]. In the case of 3(5)-trimethylsilylpyrazole only the 3-substituted tautomer is present, preventing the determination of the barrier.

Limbach *et al.* [92JA9657; 97BBPG889] made an exhaustive study of proton transfer in solid pyrazoles. For instance, the activation barriers, isotope and tunneling effects of the dimer **67,** the trimer **68,** and the tetramer **69** were determined. Catemers, like pyrazole itself, do not show dynamic behavior.



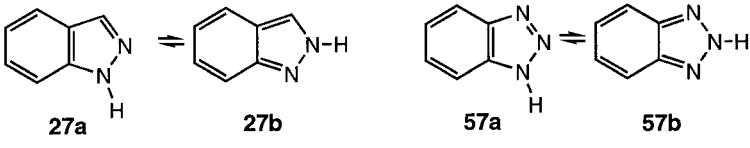
VII. Other Spectroscopic Methods

A. Microwave Spectroscopy

Contributions in this section are important because they provide structural information (geometries, dipole moments, and rotational constants) of individual tautomers in the gas phase. The molecular structure and tautomer equilibrium of 1,2,3-triazole (**20**) has been determined by MW spectroscopy [88ACSA(A)500]. This case is paradigmatic since it illustrates one of the limitations of this technique: the sensitivity depends on the dipole moment and compounds without a permanent dipole are "invisible" for MW. In the case of 1,2,3-triazole, the dipole moments are 4.38 and 0.218 D for **20b** and **20a,** respectively. Hence the signals for **20a** are very weak. Nevertheless, the relative abundance of the tautomers, estimated from intensity measurements, is **20b**/**20a** ~1 : 1000 at room temperature. The structural refinement of **20a** was carried out based upon the electron diffraction data (Section V,D,4).

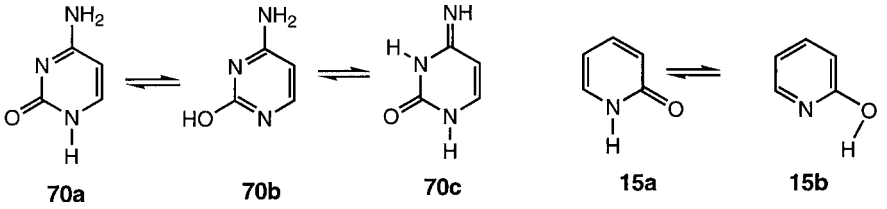
Two other azoles, indazole (**27**) and benzotriazole (**57**), have been studied by Velino and Cané. In both cases, only the 1*H*-tautomer **27a** (μ = 1.76 D) [92JSP(155)1] and **57a** (μ = 4.3 D) [93JSP(161)136] was found experimentally. In the case of indazole, this corresponds to the higher energy of 2*H* tautomer **27b** [Section III,B, 3.6 kcal mol^{-1}, 96JCS(P2)57], while in the case of benzotriazole the explanation is that the more stable 2*H*-tautomer **57b** has a μ = 0.38 D and its signals are weak and were not observed at the sensitivity used (Scheme 22) (94JOC2799).

Uracil, thymine, and cytosine have been studied using this technique (89JA2308 and references therein). For uracil and thymine, the dioxo tautomer predominates; in the case of cytosine (**70**), three tautomers were detected, **70a, 70b,** and **70c,** the last one being the least abundant. The gas-phase tautomeric equilibrium of 2-pyridone **15a** and 2-hydroxypyridine **15b** has been studied by MW spectroscopy (93JPC46) using both a conventional spectrometer and a jet-cooled millimeter-wave spectrometer. The relative abundances are 3 : 1 in favor of the hydroxy form **15b,** which exists in the *Z* conformation shown (Scheme 23).



27a **27b** **57a** **57b**

Scheme 22



SCHEME 23

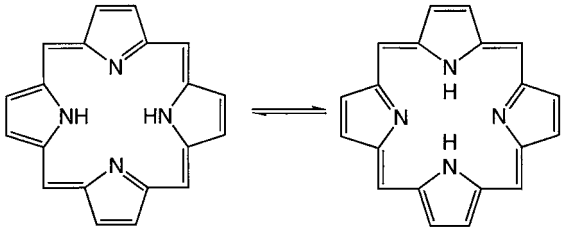
B. INFRARED AND RAMAN SPECTROSCOPY

The tautomeric proton is highly effective at making strong intermolecular HBs with other heteroatoms of the molecule. Strong HBs stabilize the crystal and produce compounds of low volatility. This can be avoided by isolating the monomers in an inert matrix. It is now much more frequent than at the time we published our previous work (76AHCS1, p. 55) to obtain spectra in an Ar or N_2 matrix at very low temperatures [e.g., 15 K (88JA8319)]. This is important for compounds, such as cytosine, which are of low volatility and for which thermal decomposition at higher temperatures makes gas-phase measurements difficult [92SA(A)811]. There are other publications where matrix isolation infrared studies are described [88JA8319; 91CPL(187)532, 91JPC2404; 92JPC1562; 95JPC6387, 95JPC14967; 96SA(A)383; 97JST(410/411)397]. The infrared study of 3-nitro-1,2,4-triazolin-5-one isolated in an Ar matrix was carried out [96JST(384)87] (gas-phase studies are precluded because this compound is a high explosive) [for calculations see (89JOC3553)].

Gas-phase studies where relevant tautomeric compounds are described are more scarce, but include uracil, thymine, and adenine [97CPL(269)39]. In the case of the 2-pyridone/hydroxypyridine equilibrium, the intensity of the OH and NH stretching vibrations was measured for eight temperatures in the range from 428 to 533 K in the gas phase. This allows determination of ΔH and ΔS for the equilibrium (92JPC1562).

New IR techniques introduced for the study of prototropic tautomerism include IR dicroism for the photoinduced double proton transfer in porphine **71** (Scheme 24) [89CPH(136)165], and IR spectroscopy in a supersonic jet (less than 50 K) for demonstrating the presence, in these conditions, of 2*H*-benzotriazole (**57b**) [96CPL(262)689].

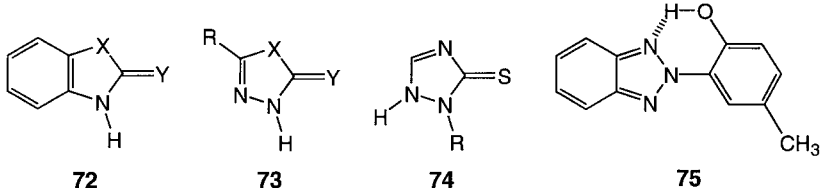
Other advances in the use of IR spectroscopy are (1) The substitution of sulfur by selenium, for comparison with the spectra of benzimidazole-, benzoxazole-, and benzothiazole-2-thiones **72** (80AJC279). (2) The use of IR as a quantitative tool to determine the association (homo- and heterodimers) of thia- and oxa-diazolin-5-thiones and -5-ones **73** (80NJC527).



71a **71b**

SCHEME 24

The authors claim that these associations, which are destroyed in "fixed" compounds, play an important role in the calculation of K_T. The cases of 1,2,4-triazole-5-thiones **74** [97SA(A)699] and of pyridone dimers **15a**–**15a** and **15a**–**15b** were also studied [96MI(13)65]. (3) The recording of IR spectra in solution at different temperatures to determine the effect of the temperature on K_T, for instance, in pyrazolinones [83JPR(325)238] and in cytosine–guanine base pairs [92MI(9)881]. (4) The determination of the equilibrium 2-aminopyridine/acetic acid 2-aminopyridinium acetate (see Section III.E) in the acid–base complex was carried out by IR (97NKK100).



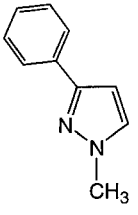
72 **73** **74** **75**

Raman spectroscopy, an invaluable complement of IR spectroscopy, has been used for tautomeric studies: imidazole-2-thione and thiazole-2-thione (89CCC2045), thiadiazolethiones (**73,** X = Y = S) [95JST(351)51], 1-phenyl-3-methyl-4-benzoyl-pyrazolin-5-one **43** [94CPL(222)559; 96MI(13)113], and 9-aminoacridine **25** [97JPC(A)283]. Elsaesser and others have reported resonance Raman studies of ground-state molecules with a highly excited vibrational system (Section VIII): Tinuvin P (**75**) [94CPL(229)340] and purine [95JST(355)147].

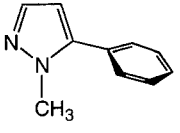
C. Ultraviolet and Visible Spectroscopy

Concerning the use of electronic spectra to study prototropic tautomerism, two preliminary comments are pertinent. The first one refers to

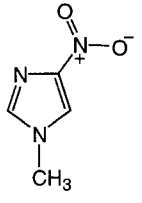
the use of fixed derivatives as model compounds. It is now clear that the replacement of the tautomeric proton by a methyl group can significantly modify the absorption if the methyl group is close to a substituent, especially one that can rotate, such as phenyl [compare **76a** (good model) vs **76b** (poor model)] (89G41; 91G477) or a nitro group [compare **77a** (good model) vs **77b** (poor model)] (92NJC511).



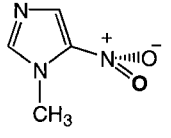
76a



76b



77a



77b

The second comment concerns the possibility of avoiding fixed derivatives, using instead the effect of the temperature on the spectrum. Assuming that the extinction coefficients are independent of the temperature, then the changes in the spectrum should correspond to changes in K_T ($\ln K_T = -\Delta H/\mathrm{RT} + \Delta S/\mathrm{R}$). Therefore, in principle it is possible to determine the equilibrium enthalpy without the use of model compounds [95ACA(314)225].

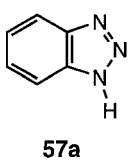
The paradigmatic case of the tautomerism between 2-pyridone **15a** and 2-hydroxypyridine **15b** has been studied several times by UV. For instance, recording the spectrum at different temperatures, UV has been used to demonstrate that both tautomers are in equilibrium in the gas phase (Section II,C) (76JA171). The same equilibrium has been studied in different solvents and the variation of K_T related to Kosower Z solvent parameters (Section II,E) [76JCS(P2)1428] as well as in supercritical fluids, where UV is a method of choice (Section II,E) (89JPC4297). The effect of concentration on the UV-visible spectra of 4-thiopyridone/4-mercaptopyridine (92JPOC191) and the tautomerism of pyridoxine [84JCS(P2)2047] and its inclusion compounds with cyclodextrins [96MI(25)113] are other examples of UV-based studies of functional tautomerism of six-membered rings. Related to these studies are those of Inuzuka reporting the study of the complexes formed by 2,6-diaminopyridine and ethanol (90BCJ216), 2-aminopyridine and acetic acid (90BCJ971), and 2,6-diaminopyridine and acetic acid (Section III,E) (92BCJ1685).

We now discuss the annular tautomerism of azoles. For 5-phenyltetrazole, the 2*H*-tautomer was found predominant in polyvinyl alcohol film (based on the determination of polarization angles of electronic transition

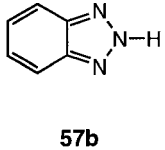
moments of both the tautomers [88ZN(A)363]). An unusual 3*H*-indole tautomer was identified by UV [94AG(E)1153]. That benzotriazole **57** exists in the gas phase as the 2*H*-tautomer **57b** was established by UV spectroscopy (93JOC5276) and then confirmed by rotationally resolved UV spectroscopy in a molecular beam [94CPL(226)305]. The effect of substituents on the exocyclic amino group of several azoles and azines on the amino-imino tautomerism has been studied by Forlani in toluene containing small amounts of DMSO or tetrabutylammonium bromide (92JHC1461).

D. Photoelectron Spectroscopy

This interesting technique, which gives information on molecules in the gas phase, has been developed significantly since our last review (76AHCS1) due essentially to the effort of the groups of Palmer and Pfister-Guillouzo. Nonetheless, because its application requires special instrumentation and knowledge, PES is, and probably will remain, exceptional as far as tautomeric studies are concerned. In general, the interpretation of the PE spectra requires both model compounds (*N*-methyl, *O*-methyl, *S*-methyl) and theoretical computations. Even so, they are subject to error. For instance, the experimental spectrum of benzotriazole **57** was explained as arising from the 1*H*-tautomer **57a** [78JST(43)203] although it is now well established that the most abundant tautomer in the gas phase is **57b** (see Sections III,E and VII,C).

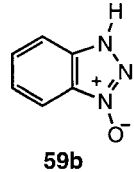


57a



57b

59a



59b

Pfister-Guillouzo established that the OH and SH tautomers are dominant for 2-, 3-, and 4-derivatives of pyridine and that only for the 2-OH and 2-SH pyridines are there significant amounts of the oxo and thioxo tautomers [77JCS(P2)1652]. The presence of 2-pyridone in the gas phase was in contradiction with previous findings using mass spectrometry (Section VII,E). The same method was used (1) to establish that 2- and 4-quinolones exist in the gas phase exclusively as NH-tautomers (81LA336), (2) to determine the structure of 2-thiouracil [90JCS(P2)871], and (3) to establish that 1-hydroxy-1,2,3-triazole exists as such in the vapor [87MI(20)105]. Taking into account that both tautomers of benzotriazole 3-oxide **59a** and **59b**

can be isolated (desmotropy) and that both present identical PE spectra (that corresponding to **59a**), the same author concluded that the equilibrium is attained in the gas phase, a point of considerable debate (Section II,C) [95SA(A)1801].

Palmer devoted several papers to simple azoles [77JST(40)191; 78JST(43)33, 78JST(43)203; 81ZN(A)1246; 87CPH(111)249], succeeding in definitely establishing the tautomeric predominance of 2*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, 2*H*-tetrazole, and 1*H*-indazole in the gas phase.

The predominance in the gas phase of the CH tautomers in the case of several pyrazolinones including one 3-aminopyrazolin-5-one was demonstrated by PES [88JCS(P2)641]; this result is consistent with previous findings (76AHCS1, p. 325). The same technique was applied to the study of the amino/imino equilibrium in 9-amino and 9-(methylamino)acridines [91MI(61)166]: although both tautomers have similar stabilities, the experimental data are in better agreement with the amino tautomer.

Recently, zero kinetic energy (ZEKE) photoelectron spectroscopy has been used to study the OH/NH tautomerism of 2-pyridone in the gas phase (95JPC8608). This work, which is expected to develop considerably, provides a wealth of information about that equilibrium for the states S_0, S_1, and D_0 (cation ground state).

E. Mass Spectrometry

Mass spectrometry has made staggering progress since the time of our previous edition (76AHCS1), but reports using this technique for tautomerism are becoming less common. One of the reasons is that now it appears that the interpretation of MS results is not as straightforward as it was once believed, even though in a recent review it was written that, "Mass spectrometry is the most informative and practical method for studying and identifying tautomers in the gas phase" [96MI(15)339]. It is interesting to note that *ab initio* calculations for MS experiments should be carried out for ground (and not excited) states.

A leading contribution to this field has been made by Maquestiau and Flammang (for two comprehensive reviews of their work see [82MI(1)237)] and [96MI(15)339]). Using various techniques such as primary isotope effects upon metastable ions (75BSB465, 75CJC490) and CID/MIKE [79BSB395, 79JCS(CC)888] they concluded that OH tautomers predominate for 3- and 4-hydroxypyridines, that SH tautomers predominate for 3- and 4-mercaptopyridines, and that NH tautomers predominate for 2- and 4-quinolones. The case of 2-hydroxypyridines was less clear: they concluded the probable existence of only the OH tautomer, but this conclusion should

be changed to reflect the predominance of this tautomer with the presence of significant quantities of the NH tautomer (Section VII,D). These results were confirmed in subsequent work by Baldwin and Langley using differences in the kinetic energy release (KER) associated with the mass spectrometric decomposition of metastable molecular ions [88JCS(P2)347] (these authors gave a good summary of previous studies). Kelley and Bernstein (89JPC643) have studied the tautomerism of the 2-pyridone/2-hydroxypyridine system in a supersonic jet expansion. They used time-of-flight mass spectroscopy (TOFMS) to characterize each tautomer and their clusters with water and ammonia. A surprising conclusion of this study is that 2-pyridone is not planar and exists in two conformations.

F. Ion Cyclotron Resonance

This technique provides quantitative information about tautomeric equilibria in the gas phase. The results are often complementary to those obtained by mass spectrometry (Section VII,E). In principle, gas-phase proton affinities, as determined by ICR, should provide quantitative data on tautomeric equilibria. The problem is the need to correct the measured values for the model compounds, generally methyl derivatives, by the so-called N-, O-, or S-methylation effect. Since the difference in stability between tautomers is generally not too large (otherwise determination of the most stable tautomer is trivial) and since the methylation effects are difficult to calculate, the result is that proton affinity measurements allow only semi-quantitative estimates of individual tautomer stabilities. This is a problem similar to but more severe than that encountered in the method using solution basicities (76AHCS1, p. 20).

Katritzky and Taft were the first to use ICR proton affinities for tautomeric studies (76JA6048). This and work of Katritzky and Nibbering (77TL1777) discuss the tautomerism of pyridones and thiopyridones and conclude that ICR results are in agreement with previous studies of Beak (76JA171)—that in the gas phase the OH and SH tautomers predominate. The complicated case of 2-thiouracil (six aromatic tautomers) was studied by Katritzky and Eyler [89JCS(P2)1499]; they conclude that the oxothioxo tautomer is the most stable.

In the field of azoles, Catalán, Abboud, and Elguero [87AHC(41)187] carried out a series of studies which show the interest of the ICR method for a case where the correction always corresponds to an N-methylation effect which can be estimated accurately. This is the case for (1) the annular tautomerism of indazole and its relationship with the annulation effect

(88JA4105) (Section V,A); (2) that of 1,2,3-triazole and 3(5)-methylpyrazole and the reason why they are liquid at room temperature (89JCC426) (Section V,D,2); and (3) the tautomerism of *C*-methyl-pyrazoles and -imidazoles (90JA1303) (Section III,B), which have already all been discussed in the present chapter. In another paper, the proton affinities of 32 *N*-H- and *N*-methyl-pyrazoles were determined by FTICR (Fourier Transform ICR) (92JOC3938). From these measurements coupled with *ab initio* calculations (Section III,C) it was possible to determine the effect of many substituents at position 3(5) (e.g., methyl, ethyl, *tert*-butyl, phenyl, nitro, amino, ethoxycarbonyl) on K_T. The tautomerism and protonation site (on the ring) of histamine has also been studied by FTICR (93JA1450).

VIII. Fluorescence Spectroscopy and Excited State Proton Transfer

This section, which received relatively limited attention in our previous monograph (76AHCS1, p. 60 and p. 529), is now a very important field of photophysics. In the present section it is discussed from the point of view of tautomerism. The energy profile of these reactions is represented in Fig. 1. The left portion corresponds to the classic Jablonski diagram (abs, absorption; isc, intersystem crossing; Fl, fluorescence; Ph, phosphorescence) and the right side contains some details about the barriers, both in the ground and the excited states, that are now accessible in several cases. Consider, for instance, an equilibrium between two tautomers that is shifted toward one of them and each tautomer differing in their electronic spectra. In the ground state, the most stable is designed $\mathbf{S_0}$ and the less stable $\mathbf{S_0'}$. Irradia-

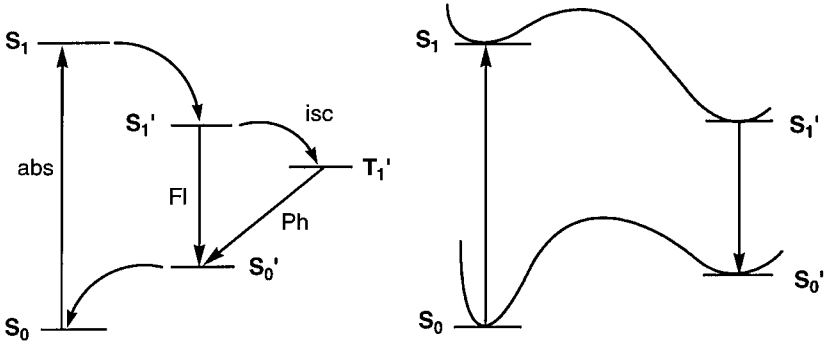


FIG. 1. Diagrams for proton transfer in the excited state

TABLE XIII
EXCITED STATE PROTON TRANSFER: MAIN AUTHORS CONTRIBUTION (LISTED BY REFERENCE)

S. K. Dogra	T. Elsaesser	J. Catalán and R. Claramunt	A. Douhal	F. R. Prieto, M. A. Rios, and M. Mosquera
83JA6223	87CPL(140)293	90JA747	94JPC12198	88CPL(146)387
86CPH(103)325	90CPL(165)28	92JA964	96CPL(256)370	94JPC8666
91BCJ3142	91JPC1918	92JA5039	96JPC149	95JPC12456
98CPH(226)285	92CPL(189)565	94JPC10606	96MI(364)383	96JPC5398
	94CPL(229)340	95JOC3427	97AG(E)1514	97JPC(A)2766
			98JPC(A)669	98JPC(A)1560
			98JPC(A)1657	

tion at the absorption wavelength of the most stable tautomer induces its transition to the singlet state $\mathbf{S_1}$ *of the same tautomer*. If the minor tautomer in the excited state, $\mathbf{S_1'}$, is more stable than in the $\mathbf{S_1}$ state, then a proton transfer will occur in the excited state (if the transfer is intramolecular, the process is called ESIPT: excited state intramolecular proton transfer). By emitting fluorescence, the ground state $\mathbf{S_0'}$ is reached, which in turn equilibrates with the major tautomer $\mathbf{S_0}$. In some cases, the triplet is formed and a phosphorescence process $\mathbf{T_1'} \rightarrow \mathbf{S_0'}$ is observed. Table XIII lists just a few of the publications of some of the authors who have contributed significantly to this field. References to three main topics in this field are collected in Table XIV.

(1) The first column corresponds to six-membered transition states where two types can be differentiated: situation **A,** where the proton transfer leads to a neutral tautomer, and situation **B** (often Tinuvin P or TIN **75**), where the proton transfer leads to a zwitterionic tautomer (Scheme 25).

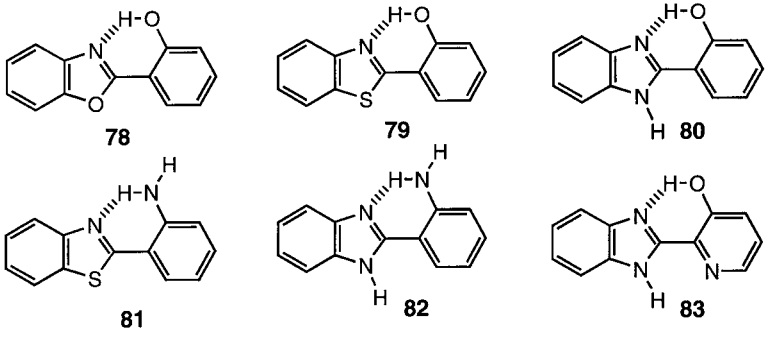
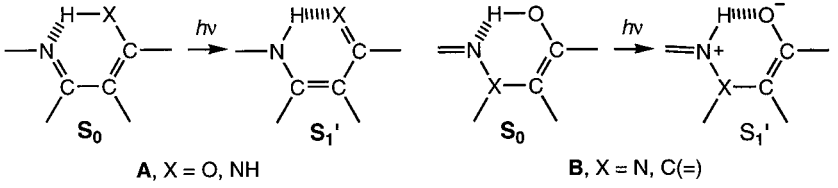


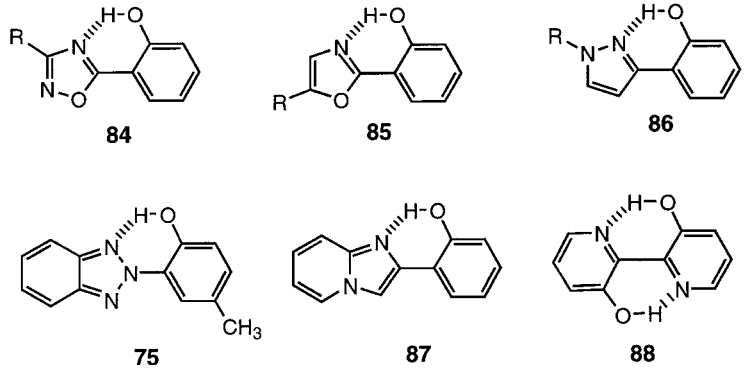
TABLE XIV

EXCITED STATE PROTON TRANSFER: MAIN TOPICS EXPLORED (LISTED BY REFERENCE)

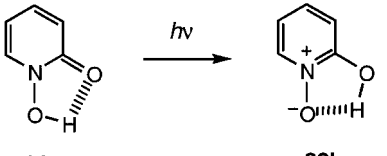
Intramolecular (ESIPT) (**A** or **B**)	Intermolecular 7-azaindole	Intermolecular Other heterocycles
85JA1561 (**A: 78**)	81MI(24,25)519	82JPC49 (adenine)
87CPL(140)293 (**A: 79**)	82CPL(93)204	82JPC2418 (pyridobenzimidazole)
88CPL(146)387 (**A: 78**)	83JPC3202	83JA6223 (indazole)
90CPL(165)28 (**B: 75**)	84JPC5840	84JA850 (hydroxyquinoline)
90JA747 (**A: 80** and **B: 75**)	84JST(114)359	84JCS(CC)435 (pyridone)
90MI(40)654 (**B: 75**)	86CPL(125)581	85JCS(P2)1423 (pyridone)
91BCJ3142 (**A: 81**)	87JA1346	85JPC399 (indazole)
91CPL(185)206 (**B: 88**)	88JCS(F2)1163	86CPH(103)325 (indazolinone)
91JPC1918 (**B: 75**)	88JPC6545	87AHC(41)187 (azoles)
92CPH(163)43 (**A: 78**)	92JA8343	88JPC1760 (uracil, thymine)
92CPL(189)565 (**B: 75**)	92JPC5203	89JCS(F2)1539 (aminopyridine)
92CPL(198)443 (**A: 80**)	92JPC8430	90JPC8536 (pyridobenzimidazole)
92JA964 (**B: 75**)	93JPC1770	91JPC2404 (pyrimidinethione)
92JA5039 (**A: 86**)	94MI(568)182	93CPL(207)513 (hydroxyquinoline)
92JPC2018 (**A: 84**)	95JPC11994	93CPL(211)293 (pyridone)
92JPC10225 (**B: 75**)	96CPL(256)370	93JA9708 (pyridone)
93JPC306 (**A: 78**)	97CPL(277)340	93JPC13615 (hydroxyquinoline)
93JPC8952 (**A: 78**)	98JPC(A)669	94JPC10606 (indazole)
94CPH(184)261 (**A: 78**)	98CPL(287)1	96CPH(213)193 (pyridone)
94CPL(229)340 (**B: 75**)	98CPL(293)515	96JPC149 (hydroxyquinoline)
94JPC8666 (**A: 83**)	98JPC(A)669	96JPC3933 (pyridone)
94JPC9126 (**A: 78** and **A: 80**)		97JCS(F)1297 (aminoacridine)
94JPC12198 (**A: 85**)		97NKK393 (aminopyridine)
95CPL(239)282 (**B: 88**)		97SA(A)1723 (aminoacridine)
95JOC3427 (**A: 86**)		98CL169 (2-(pyrrolyl)ethenyl)
95JPC12456 (**A: 78**)		
95JPC17711 (**A: 80**)		
96CPL(252)33 (**B: 88**)		
96CPL(256)536 (**A: 78**)		
96JPC5398 (**A: 80**)		
96MI(364)383 (**A: 85**)		
96THE(368)17 (**B: 88**)		
97AG(E)1514 (**B: 87**)		
97JCS(P2)1861 (**A: 78**)		
97JPC(A)2766 (**A: 80**)		
97JPC(A)7948 (**A: 78**)		
98CPH(226)285 (**A: 82**)		
98JPC(A)1560 (**A: 79**, **80**)		
98JPC(A)1657 (**A: 85**)		



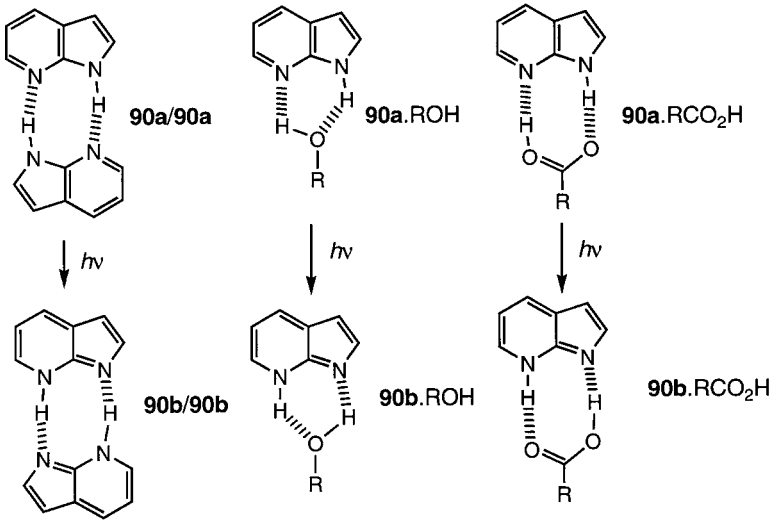
SCHEME 25



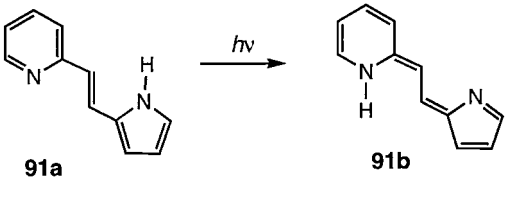
A rare case of ESIPT that does not belong to these types is the five-membered cyclic transfer observed by Sakurai in 1-hydroxy-2-pyridone (**89**) (Scheme 26) [81JCS(CC)1004, 84JCS(P2)2031]. (2) The second column corresponds to 7-azaindole (**90**) [82CPL(93)204; 92JA8343; 93JPC1770] and related compounds such as 1-azacarbazole [82CPL(93) 204; 84JST(114)359] and 7-azatryptophan [92JA8343; 93JPC1770]. The three main mechanisms explored are shown in Scheme 27. The formation of exciplexes has been observed with alcohols and water (R = H). The most recent papers [98CPL(287)1, 98JPC(A)669] provide a state-of-the-art summary of the photophysics of 7-azaindole. (3) The cases reported in the third column are less coherent. There are some examples of intermolecular proton transfer assisted by acetic acid similar to those of Scheme 27; for instance, from 1*H*- (**27a**) to 2*H*-indazole (**27b**) (85JPC399) and from 2-amino- to 2-imino-pyridine [89JCS(F2)1539]. Others deal with the determination of pK_as in the excited state using the Förster's cycle [86CPH(103)325], a procedure that has been criticized [87AHC(41)187]. Among the many interesting cases, we single out the phototautomerization process (**91a** → **91b**) studied by Arai (Scheme 28) (98CL169).



SCHEME 26



SCHEME 27



SCHEME 28

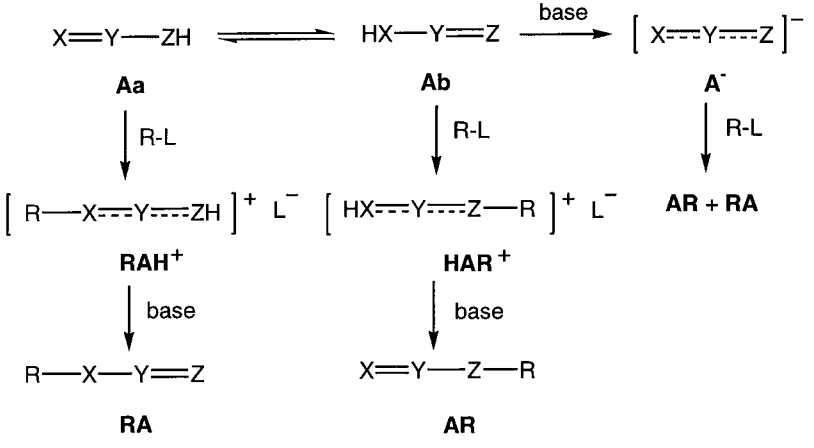
IX. Tautomerism and Aromaticity

There is an intimate relationship between tautomerism and aromaticity as the designation "heteroaromatic tautomerism" reflects. The problem was clearly perceived at the time of our previous monograph (76AHCS1, p. 73 and p. 551), but since then the subject has been extensively developed in one of our groups. In a series of papers, Katritzky, Cook, Barczynski, Szafran, and Musumarra *et al.* reviewed the situation of pyrrole, furan and thiophene (76T1767), pyrazole and isoxazole (78T1571), the whole concept of aromaticity [89JA7], five- and six-membered rings [89JA7; 90JPR(332)853], benzo-fused five- and six-membered rings [90JPR(332)870], less familiar heterocycles [90JPR(332)885], aromaticity indexes (90TCM247), and azaannulenes (93H2483). Catalán *et al.* have related the tautomerism of pyrazoles **3,** indazoles **27,** 1,2,3-triazoles **20,** and benzotriazoles **57** to the aromaticity of the "benzenoid" and "quinonoid" forms and to the adjacent "lone-pair/lone-pair" repulsion [89JA7348; 94JOC2799; 96JCS(P2)57]. Important early contributions were also made by Beak (76JA171).

A difficulty in relating tautomerism and aromaticity precisely is that K_T is a thermodynamic value related to physics while aromaticity remains a somewhat fuzzy notion, essential to chemistry, but difficult to quantify. Indeed, aromaticity was demonstrated by one of us to be a multidimensional characteristic with "magnetic" and "classic" components that are essentially orthogonal (89JA7). This conclusion that aromaticity is multidimensional was supported independently by the work of Jug (91JPO163) and Krygowski (95JCI203; 96T10255). Although it was disputed by Schleyer [95AG(E)337; 96PAC209], the conclusion has recently been decisively reaffirmed (98JOC5228).

X. Tautomerism and Reactivity

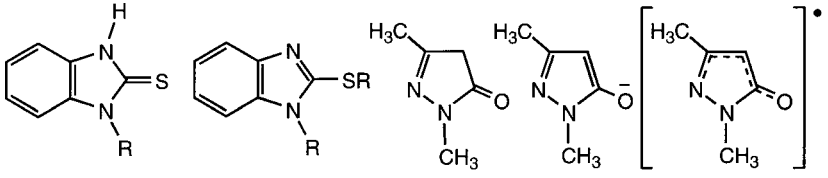
Our previous treatment (76AHCS1, p. 12) contained a section called "Chemical Methods to Study Tautomerism" where the relationship between tautomerism and reactivity was discussed. Today, nobody uses chemical methods to study tautomerism. However, a great many reactions are carried out on tautomeric heterocycles, although few papers contain new insights on that topic. Authors desiring to explain reactivity results based on tautomerism must take great care to verify that the substrate is in the neutral form **AH** and not as a conjugated anion $\mathbf{A}^-$ or cation $\mathbf{HAH}^+$**,** which are usually devoid of tautomerism. They must also realize that most frequently the reaction path from tautomers to products in-



SCHEME 29

volves a change of structure, from **Aa** to **RA** and from **Ab** to **AR** (Scheme 29) (from 78JOC1367).

This elementary principle is frequently neglected. Thus, for instance, the alkylation of benzimidazolin-2-thione (**92,** R = H) in the presence of an alkali to obtain an SR derivative **93** (R = substituent) was assigned as a reaction of the thiol **93** (R = H) [82JHC681]; instead it is a reaction of the mesomeric anion, which results from the deprotonation of either the thiol or the thione. Moreover, the formation of an N-R derivative (**92,** R = substituent) in anhydrous conditions was given as a proof that the compound reacted predominantly as the thione. The truth is exactly the contrary; the alkylation of the neutral thione species can only take place on the lone pair of the sulfur and, therefore, an SR derivative should be obtained: the formation of an N-R derivative must be a reaction of either the thiol or the mesomeric and ambident anion. The same misconception is also apparent in a study of the alkylation of pyrazolinones (3-trifluoromethyl and 3-methyl), where reactions carried out in DMF in the presence of K_2CO_3 (formation of OR and CR derivatives) were related to the respective tautomeric compositions (93H1375). Another common mistake is to assume that the most abundant tautomer should be the most reactive, whereas frequently the more abundant tautomer is the less reactive (76AHCS1, p. 13; 78JOC1367). To illustrate this second misconception, the radical **96** was calculated (B3LYP/6-31G*) to be formed from the anion **95** and not from the neutral molecule **94** on the grounds that **94,** the most stable tautomer, is less reactive than the anion **95,** when the other tautomers, the NH and the OH, are more reactive than the CH one (although probably each is less reactive than the anion towards one-electron oxidation) [97JPC(A)3769].

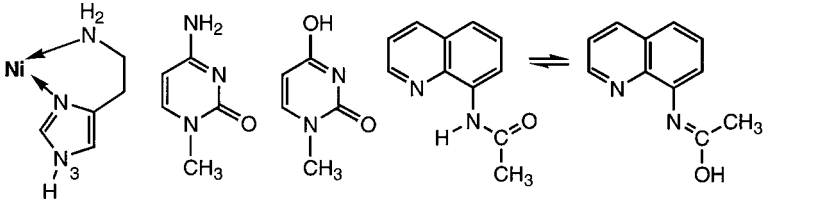


92 **93** **94** **95** **96**

Beak (78JOC1367), in an illuminating paper, proved that methyl fluorosulfonate reacts with tautomeric compounds regiospecifically at the heteroatom remote from the mobile proton; thus, 2-methoxypyridines are obtained from 2-pyridones if isolation of the salts $\mathbf{RAH}^+$ are followed by treatment with base. Other papers, where the situation is clearly understood, deal with (1) the rates of alkylation of histidine and their relation to tautomeric composition and steric effects [83ACSA(B)809], (2) the kinetics (stop-flow) of bromination of 4-pyridone (**16a**) and the corresponding *N*-methyl and *O*-methyl derivatives (83CJC2556), (3) an interesting study of the reaction between 2-pyridones and benzyne (formation of Diels–Alder plus Michael-type adducts) (85BCJ1149), (4) the reduction of dihydro- into tetrahydro-pterines (76AHCS1, p. 165; 85JA6689), and (5) the relationships between tautomerism and sensitivity to shock or impact of the explosive ANTA (3-nitro-5-amino-1,2,4-triazole, Section III,B) [94MI(19)32]. Two high-level theoretical papers by Jursic and Zdravkovski [95JOC2865, 95THE(337)9] discussed the relationship between the tautomerism of imidazole and tetrazole **22** (including nonaromatic tautomers) and their Diels–Alder reactivity toward ethylene and singlet oxygen.

XI. Tautomerism in Organometallic and Coordination Chemistry

We have collected data from papers which, in one way or another, report results relating heterocyclic tautomerism with metals. Thus, the two histamine tautomers $\mathbf{14aH}^+$ and $\mathbf{14bH}^+$ react with $Ni(OH_2)_6^{2+}$ at different rates, the 5-substituted tautomer $\mathbf{14bH}^+$ being slower (85IC2721). Since only one of them has a chelated structure **(97)**, the equilibrium between **14a** and **14b** (Section III,B) is shifted completely toward **14a** on complexation (for the similar case of carnosine and Cd(II) see [97JCR(S)304]). Complexation with Zn^{2+} reversed the equilibrium in the case of 4(5)-methylimidazole (**17**) from 0.8 kcal mol^{-1} in favor of the 4-methyl tautomer (**17a**) to 1 kcal mol^{-1} in favor of the 5-methyl one (**17b**) [87IJQ(31)405]. Lippert has described the stabilization of rare tautomers of nucleobases by platinum: the iminooxo form of 1-methylcytosine (**98**)



97 **98** **99** **100a** (amide form) **100b** (iminol form)

SCHEME 30

(86JA6616; 98CEJ397) and the 2-oxo-4-hydroxy form (**99**) of 1-methyluracil (89JA7213) (Scheme 30). Chelating heterocycles such as 1-aryl-3-aroylamino-pyra-zolin-5-ones (89RJIC1695) and 3-aryl-4-aroylisoxazolin-5-ones [96MI(14)653] change their tautomeric composition on complexation.

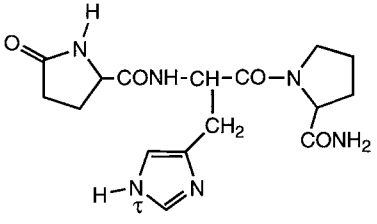
The problem is not always clearly understood. For instance, it was stated (96ACR348) that, "In fact, the amide **100** does not bind directly to the metal (Ir) in the amide form **100a** but *first* tautomerizes to the very rare iminol form **100b** before binding to the metal *via* the nitrogen lone pair." A simple calculation (AM1) shows that **100a** is 11 kcal mol^{-1} more stable than **100b;** therefore, it is much more probable that either (1) the coordination first intervenes and then the tautomerization occurs or (2) that proton transfer from the NH to the Ir first occurs, followed by coordination of the anion and proton transfer from the Ir to the oxygen.

XII. Tautomerism and Biological Activity

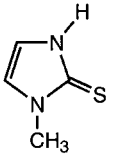
No serious attempt has been made to study the relationship (if any) between tautomerism and biological properties in the sense to change progressively K_T (by substitution) and to determine if the biological response varies, linearly or not, with K_T. The problem is that the substituents that modify K_T can also modify the biological response without having a causal relationship. Two other ways to change K_T (variations of solvent and temperature) are not applicable in biological tests.

This is not to say that the tautomeric composition of drugs and related compounds is irrelevant. For instance, it has been hypothesized that the tautomeric change of histamine (Section III,B) is part of the mechanism of action at H_2 receptors [79MI(14)9] and that the difference between agonists and antagonists could be related to tautomerism (87JCPB633). In the case of the tripeptide thyroliberin **101,** the imidazole annular tautomerism of the histidine fragment is a key factor for hormonal activity and that the N(τ)-H tautomer must be considered as the biological form of thy-

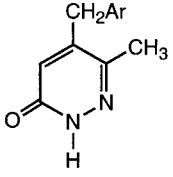
roliberin [86MI(14)405]. The mutagenic action of some compounds has been rationalized as implying the tautomerization of bases like adenosine [82MI(139)69] although other authors have disputed this conclusion [83MI(16)479]. In structure–activity studies it is important to use the correct tautomer (i.e., the tautomer present under physiological conditions); this has been pointed out concerning methimazole **102** [a thione (94BMCL1357)], a series of aromatic pyridazine tautomers **103** (95AJC1601), and in isoxazol-3-ols and isothiazol-3-ols as carboxy group bioisosters [97JCS(P2)1783].



101



102



103

XIII. Tautomerism and Supramolecular Chemistry

There are cases where the tautomerism is not studied per se but where one tautomer is used to build up supramolecular assemblies. This topic deserves a review in itself because most supramolecular assemblies use as scaffolds heterocyclic compounds in a specific tautomeric form. Outstanding contributions to this section are the publications by Whitesides where he uses as monomers 2-aminopyrimidines, melamines, maleic hydrazide and dipyridones (90JA9025; 94CR2383; 95ACR37), and, more recently, benzimidazolones (96JA4018). Other authors have also used benzimidazolones to prepare supramolecular host compounds (97CC1461, 97T7689).

The mechanism of recognition of most supramolecular entities (such as abiotic receptors) is the formation of several hydrogen bonds. Since heterocyclic tautomers possess both strong HBA and HBD properties (see Sections III,G, V,D,2, and VI,G), they are often used for this purpose. For instance, the hydrogen bond network formed by 5,5′-linked bis(2-pyridones) has been used by Dickert to obtain sensors (96BBG1312).

XIV. Criteria for Choice of Physical Methods

A. Introduction

The reader is referred to our previous monograph (76AHCS1, p. 68); most of what was written there is equally valid today.

B. Solid State

As already explained in the relevant section, the use of X-ray crystallography (Section V,D,2), the possibility to determine the molecular structure from powder diffraction without the need to obtain monocrystals, and the many variants of solid-state NMR (Section VI,F) have profoundly enhanced the study of tautomerism in the solid state.

C. Vapor Phase

The determination of molecular structure by microwave spectroscopy (Section VII,A), the measurement of acid–base equilibria by ICR (Section VII,F), and theoretical calculations, especially accurate for the gas phase, are the main novelties of this section.

D. Liquid Phase

All the classic methods apply here, nothing very new has appeared, although some "exotic" nuclei in NMR have been applied to the study of tautomerism.

E. Quantitative Determination of K_T Values

If the barrier is large enough and the populations of tautomers are not too different, the method of choice is ^{1}H NMR and integration of some well-resolved signals. If the populations are very different, it is sometimes possible (if one knows where the signal is expected to appear) to observe less than 1% quantities of the minor tautomers, but the integration of signals of such different intensities is not precise. If the equilibrium is too fast on the NMR time scale, then it is necessary to resort to interpolation methods using spectroscopic or thermodynamic data, e.g., pK_a values (76AHCS1). Due to the accuracy of high level *ab initio* calculations and the progress in the inclusion of solvent effects, it can be considered that this approach is also a method of determining K_T values.

XV. Conclusions

On the whole, the four main changes from the previous review (76AHCS1) have been (1) the standard application of high-level theoretical methods, (2) the massive use of X-ray crystallography, (3) the introduc-

tion of solid-state CPMAS NMR, and (4) the increasing significance of proton transfer in the excited state. Today, the normal attitude when publishing a new study of tautomerism is to accompany it by some computations in order to verify that the result is consistent. Not that the comparison is always easy (for instance, when the experimental results concern the solid state), but progress in this direction is unstoppable.

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Tautomerism of Heterocycles: Five-Membered Rings with One Heteroatom

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I. Introduction

Great progress has been made in the experimental and theoretical investigation of tautomerism of five-membered ring systems since 1975, and a number of reviews dealing partly or entirely with this subject have appeared since then. In Table I some pertinent references are given.

In addition to these reviews, the following studies are of general interest: tunneling graphs in intramolecular proton transfer reactions (91JPC10457) and comparison of theoretical models of solvation (96MI5). For further reviews on molecular rearrangements (tautomerism included) see A. W. Murray (84MI1; 86MI2; 87MI1). See also Chapter 1 of the present volume for general references.

TABLE I

REVIEWS AND GENERAL STUDIES DEALING WITH TAUTOMERIC STUDIES OF HETEROCYCLIC COMPOUNDS

Topic	Reference
Theoretical study of the effects of molecular structure and solvation on tautomeric equilibria (SCF-MO-PPP)	75JST237
^{14}N NMR of nitrogen heterocycles	78OMR27
Recent progress in the investigation of the tautomerism of organic compounds	80MI1
Molecular design of tautomeric compounds	81ACR210; 88MI2
Theoretical study of tautomerism of five-membered heterocycles (HMO)	81MI1
Concepts of tautomerism	83MI1
Analysis of substituent effects on tautomeric equilibria by the method of perturbed molecular orbitals	83MI2
Theoretical studies of heteroaromatic compounds (MNDO, 4-31G)	85JOC4894
Quantum chemical predictions of tautomeric equilibria	86MI1
Ab initio multireference CI studies of tautomers; UPS spectra	87MI4
Combined approach to the tautomerism in azaaromatic heterocycles by N, C, and H NMR	87MI1
Fluoro-azoles: Experimental data and MNDO studies	88H1803
Tautomerism: A review	88MI1
Thermochemical investigations of tautomeric equilibria; solvent effects	89MI1, 89MI2; 90MI1
Theoretical aspects of the study of prototropic tautomers by mass spectrometry	89MI3
Generation of reaction networks with RAIN; resonance structures and tautomerism	90MI1
Solid-state NMR studies of reversible 1,5-H shifts	90MI2
Tautomeric equilibria (AM1, MNDO, PM3)	90ZN(A)1328; 91MI2
Prototropic tautomerism of heteroaromatic compounds	91H329
AM1-SM1 for tautomeric equilibria	91JA8552
Resonance energies and tautomerism of substituted aromatic heterocycles and their benzo derivatives	91MI1
Reaction-field-supermolecule approach to calculation of solvent effects	92JCS(F1)189
Prediction of tautomeric equilibria by a quantum mechanical continuum model of solvation	93MI1
Tautomerism of thiophenes	94KGS1445
Tautomerism and isomerism of heterocycles (part 1)	95H1805
Tautomerism and isomerism of heterocycles (part 2)	95H2057
Application of mass spectrometry for the analysis of tautomeric compounds	96MI1
Tautomeric interconversions of heterocyclic compounds	96MI2
Algebraic characterization of the thione-thiol prototropic tautomerism	96MI3

(*continues*)

TABLE I—*Continued*

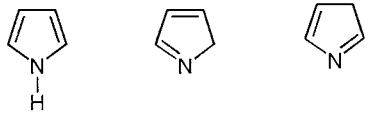
Topic	Reference
Tautomerism of heterocyclic thiols	96RCR307
Application of the Hammett equation to proton transfer reactions	96MI4
Substituent effects on the ^{15}N NMR parameters of azoles	97MI1
Theoretical studies: The prototropic tautomerism of nitrogen bases (AM1)	97MI2
Molecular properties and spectra in solution	97MI3
Solvent effects on tautomeric equilibria in heterocycles, a theoretical study	97MI4
Geometry optimization of molecular structure in solution by the polarizable continuum model	98MI1

II. Annular Tautomerism of Five-Membered Rings

A. Neutral Molecules

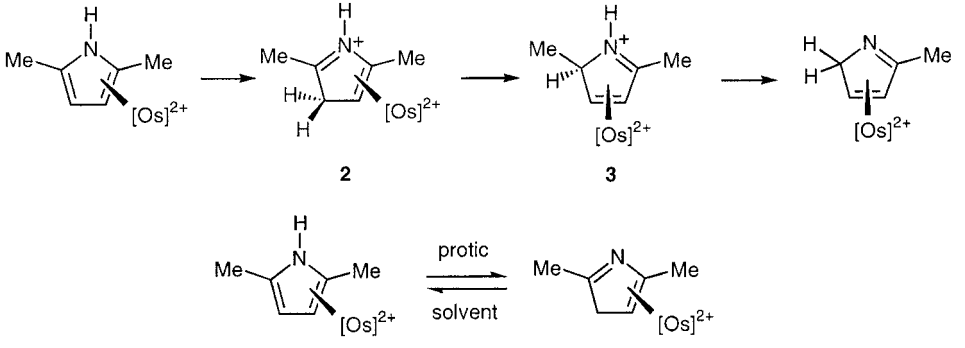
1. *Pyrroles*

As has been pointed out earlier (76AHCS1, p. 215), 1*H*-pyrrole **1a** and its simple derivatives are far more stable than the corresponding pyrrolenine forms **1b** and **1c.** Recent studies confirm these experimental results (90HC1, 90HC549; see also 82JOC5132; 97MI1).



1a **1b** **1c**

Semiempirical and *ab initio* calculations are in accordance with this observation (84CS84; 86BSF429) [basis set effects have also been investigated (86JPC5597)]. Recent DFT calculations (B3LYP/6-31G*) reveal the following energies (in hartrees): **1a,** –210.16589; **1b,** –210.14676; **1c,** –210.14296 (99UP1). Kinetic studies of the 1,2-sigmatropic hydrogen shift in the photorearrangement intermediate of *N*-acetylpyrrole have been reported [97JPC(A)459]. Structures and tautomerism energies of pyrrole and some pyrrole derivatives have also been calculated by the MINDO/3 method (79JOC374). Semiempirical studies of oligopyrroles (and oxidized derivatives) have been reported (99MI1). Pyrrole was found to form η^2-complexes with pentaamminoosmium(II) when $(NH_3)_5Os(OTf)_3$ is reduced over Mg^0 in the presence of an excess of the heterocycle (Scheme 1) (89JA5969). Homonuclear decoupling at –25°C reveals a dynamic process in which the metal tautomerizes between the 2,3- and the 4,5-η^2-positions in

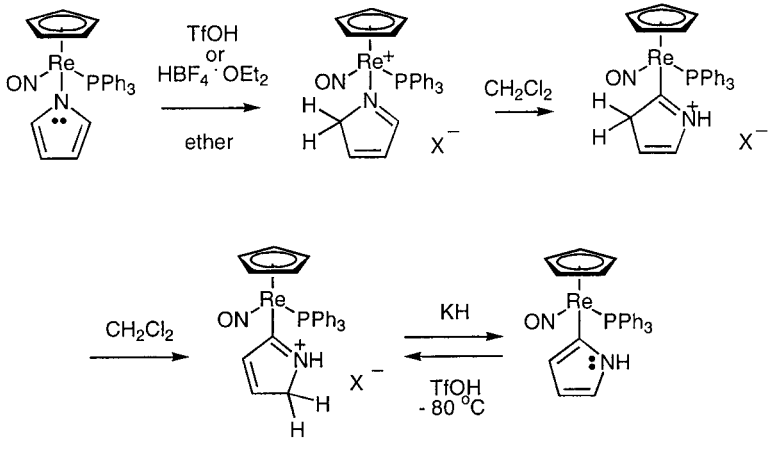


SCHEME 1

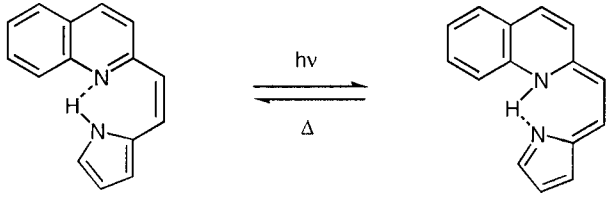
the pyrrole ring. An X-ray structure of the corresponding 2,5-dimethylpyrrole derivative was reported (91JA6682). Further studies have shown (92JA5684) that, in contrast to the free ligands, complexes of this type can be protonated chemo- and stereoselectively at the β-carbon atom, farthest from the metal, to produce pyrrolium species (**2** and **3**), whose acidities range in pK_a from 4.2 to 7.5. In the presence of a weak base some of those 3*H*-pyrrolium species could be converted to the 2*H*-pyrrolium tautomer.

On dissolving the complex in a protic solvent (e.g., water) a significant amount of the 3*H*-tautomer is formed (95JOC2125).

Many transition-metal pyrrolyl-*N*-complexes have been synthesized. In a recent study an *N*-complex with the chiral rhenium fragment $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$ was prepared. On treatment with TfOH and $HBF_4\text{-}OEt_2$ a protonation at C-2 occurs to give a crystalline 2*H*-pyrrole tautomer. This compound rearranges in solution to a carbon–ligand species (Scheme 2) (93OM4728).



SCHEME 2



4 **5**

A photoinduced hydrogen atom transfer in *cis*-1-(2-pyrrolyl)-2-(2-quinoline)ethene was reported (94JA3171). The rate constant k (**5** → **4**); increases with increasing temperature from $2.1 \cdot 10^6$ s^{-1} at 15.8°C to $7.7 \cdot 10^6$ s^{-1} at 39.5°C, giving an activation energy of 9.4 kcal/mol.

For similar studies with pyrrolyl-quinolylethenes and pyridinyl-pyrrolylethenes see 94JA3171 and 98CL1153.

2. *Indole–Indolenine*

Indole exists overwhelmingly in the 1*H*-indole form as do other simple indoles (76AHCS1, p. 216). However, the tendency for indolenines to exist is considerably greater than that for pyrrolenines. In accord with this observation, differences in the heat of formation ($\Delta\Delta H_f^0$) and energies (ΔE) between 1*H*-indole and 3*H*-indole (indolenine) are far less than for the corresponding pyrrole tautomer ($\Delta\Delta H_f^0 = 2.4$ kcal/mol [AM1]). DFT results are given in Table II (99UP1).

At the time of the previous review (76AHCS1), 3*H*-indole was unknown. Recently it was found that this compound is formed when an etheral solution of 2,3-dihydro-*N*-indolylacetophenone is irradiated at 308 or 313 nm

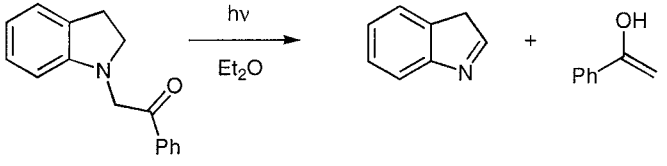
TABLE II

Ab Initio Results for 1*H*-Indole and 3*H*-Indole (Energies in Hartrees) (99UP1)

Method	1*H*-indole	3*H*-indole	Δ^a
B3LYP/6-31G*	−363.81669	−363.80496	7.4
B3LYP/6-311G(d)	−363.89431	−363.88065	8.6
B3LYP/6-311++G(d, p)	−363.91400	−363.89750	10.4
B3LYP/6-311G(3df, 3dp)//6-311++G(d, p)	−363.93916	−363.92102	11.4

[a] ΔE in kcal/mol.

(Scheme 3). At –100°C this compound is stable but it tautomerizes to 1*H*-indole rapidly at –50°C. In a slightly basic solution (pH ≈ 9, 25°C) the compound is remarkably stable ($\tau \sim 100$ s). The equilibrium constant was determined to be $pK_T = 5.8 \pm 0.2$ [ΔG (aq, 298 K) = 33 ± 1 kJ mol^{-1}] (7.9 ± 0.2 kcal/mol) (94AG1240).



SCHEME 3

Thermal isomerization and decomposition reaction of indole behind reflected shock waves at 1050–1650 K have been explained by a preequilibrium between 1*H*-indole and 3*H*-indole (97JPC(A)7787).

3. *Isoindole–Isoindolenine*

As was pointed out earlier (76AHCS1, p. 217), tautomeric equilibria for substituted isoindole–isoindolenine systems depend critically upon the substituents. Isoindole exists in the *o*-quinoid form **6.** Computational results for the parent systems are given in Table III (99UP1). The results indicate that within the B3LYP functional only large basis sets provide reliable energy differences.

Electron-releasing substituents stabilize the isoindolenine tautomer **7,** whereas electron-withdrawing groups have the opposite effect. In Table IV some data are given.

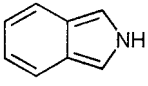
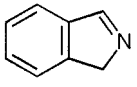
1,3,4,7-Tetramethyl-1*H*-isoindole exists in an equilibrium with its tautomer. The kinetics of this transformation in water or deuterium oxide at various pH or pD at 25°C were measured spectrophotometrically. From the considerable isotope effect and the fact that the 1-position of the isoindole is electron rich it was concluded that this tautomerization may include the protonation at the 1-position as the rate-determining step (92MI1). 4,5,6,7-Tetrachloroisoindole exists entirely as isoindole (76TL1661).

5-Pivaloylisoindole has been obtained as a stable crystalline substance. According to the ^{1}H and ^{13}C NMR spectra, this compound exists entirely as isoindole ($CDCl_3$, [D_6]-DMSO, [D_5]-pyridine, [D_6]-acetone) (82AG634).

3-Alkoxyisoindoles bearing substituents at the carbocyclic ring exist exclusively in the benzenoid structure; the *o*-quinoid form could not be detected spectroscopically (88CB243). 3-(Methylthio)isoindoles are far more reactive than the corresponding alkoxy-isoindoles. These compounds prefer the benzenoid structure, too (88CB243).

TABLE III

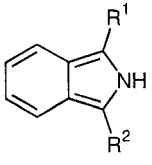
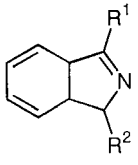
SEMIEMPIRICAL AND *AB INITIO* RESULTS FOR ISOINDOLE AND ISOINDOLENINE[a,b]

Method	Isoindole	Isoindolenine	Δ^c
			
	6	**7**	
AM1	61.51	59.52	−2.0
PM3	47.49	46.52	−1.0
B3LYP/6-31G*	−363.80184	−363.80523	+2.1
B3LYP/6-311G(d)	−363.87971	−363.88051	+0.5
B3LYP/6-311++G(d, p)	−363.89948	−363.89748	−1.3
B3LYP/6-311G(3df, 3dp)//6-311++G(d,p)	−363.92450	−363.92082	−2.3
B3LYP/6-311G++(3df,3dp)// 6-311++G(d,p)	−363.92795	−363.92482	−2.0

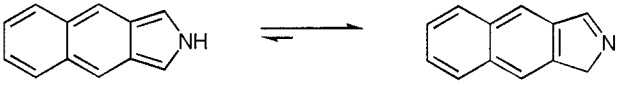
[a] ΔH_f^0 in kcal/mol
[b] E in hartrees.
[c] Values in kcal/mol

TABLE IV

EFFECT OF SUBSTITUTION ON THE ISOINDOLE–ISOINDOLENINE EQUILIBRIUM

R^1	R^2	% **8**	% **9**	Reference
				
8			**9**	
H	H	100	0	77TL1095
Me	H	1	99	79T1055
Me	Me	20	80	79T1055
Ph	H	91	9	74JA3648
Ph	Ph	100	0	75CC272
CO_2Et	H	100	0	75S252
CO_2Et	CO_2Et	100	0	75S252
OEt	H	0	100	74JA3648; 88CB243

Benz[*f*]isoindole **10** exists, on the basis of spectroscopic examination, predominantly in the benzenoid tautomeric form **10b,** although the formation of the Diels–Alder adduct with *N*-phenylmaleimide suggests the presence of a small amount of the *o*-quinoid tautomer **10a** (78JOC4469).



10a **10b**

B. Conjugate Acids

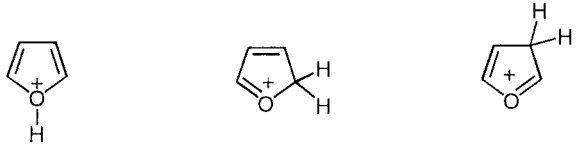
1. *Furan, Pyrrole, and Thiophene Cations*

It is well established that in solution electrophilic substitution of pyrrole and furan takes place predominantly at C-2. Recent ion cyclotron resonance experiments have confirmed that the protonation site of these compounds preferred thermodynamically in the gas phase is also the C-2 position (80AG934; 81NJC505; 82JA7084, 82JA7091). Different theoretical approaches have been used to predict the preferred protonation in furan (and other heterocycles) (75T915; 78T275; 81NJC505; 82T3693; 83T2851; 84JA421).

Recent *ab initio* calculations (6-31G*//3-21G) (see Scheme 4) confirm the experimental observation that protonation of furan occurs exclusively at C-2 [86JCS(P2)147].

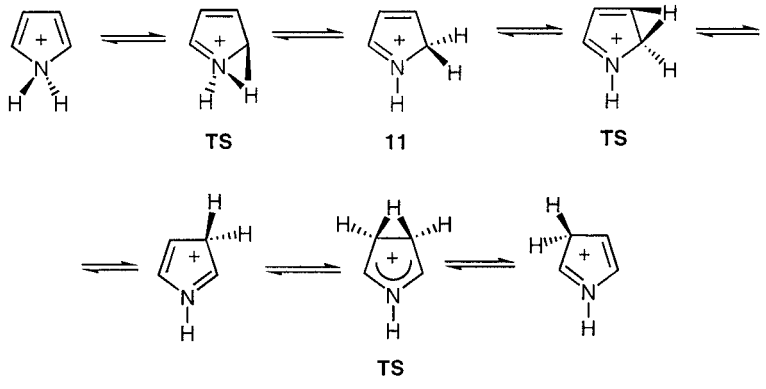
Predicted proton affinities of azoles (and oxazoles) calculated with simple *ab initio* methods (STO-3G) are reported to differ little from 6-31G** values (89KGS508).

The potential surface of protonated pyrrole (see Scheme 5) was analyzed for minimums and saddle points with the CNDO/2-FK and MNDO/2 methods. The α-protonated species **11** was found to be the most stable one in this series (80JPR147).



- 228.90276	- 228.96480	- 228.94162	(in hartrees)
38.9	0.0	14.5	(in kcal/mol)

Scheme 4. *Ab initio* results for protonated furans [86JCS(P2)147].

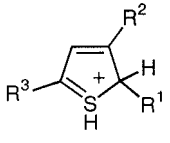


SCHEME 5

DFT calculations for other heterocycles (neutral azoles, protonated forms) have been reported (94T2405, for semiempirical calculations see 93ZOR1297; see also AM1, MNDO, and PM3 calculations for neutral five- and six-membered nitrogen heterocycles).

Thiophenes are protonated at C-2. The ^{1}H NMR spectra of a number of protonated alkylthiophenes have been reported (86T759).

Selected values are given in Scheme 6.

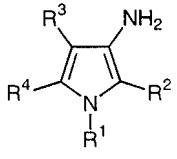


R^1	R^2	R^3	δ (H-2)[a]
H	H	Et	5.29
H	Et	Et	5.12
Et	H	Et	5.42
Et	Et	Et	5.24

[a] Thiophenium ions were prepared with $AlCl_3$/HCl in CD_2Cl_2.

SCHEME 6

The protonation of 3-aminopyrroles **12** has been investigated using ^{1}H and ^{13}C NMR spectroscopy. According to these data the protonation occurs at the amino group with no evidence for protonation of the pyrrole ring (87T5225).



12

R^1	R^2	R^3	R^4
H	Ph	H	Me
H	Ph	COMe	Me
H	Ph	CO_2Et	Me
Me	Ph	CO_2Et	Me
H	Ph	H	Ph

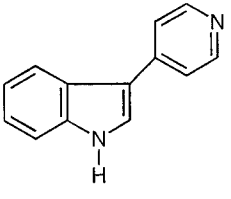
2. *Cations of Benzo Derivatives*

The acid–base equilibria of protonation (and deprotonation) of pyrrole, indole, and the corresponding *N*-methyl derivatives have been reexamined using the "Excess Acidity Method" (EAM) (89T7501). In most cases, values only slightly different from those previously reported were found except for indole; EAM yielded a pK_a value of -2.43. Protonation (and deprotonation) studies of a set of 4-substituted indoles have also been reported (91H1123). Theoretical investigations (STO-3G of INDO optimized geometries) of protonation of methylindoles reveal that the most basic site is C-3, in agreement with experimental data (82T3693). DFT calculations confirm these results. The energy differences between the C-3-protonated form and the N-protonated cation for indole amount to 15.7 (B3LYP/6-31G*) and 13.7 kcal/mol [B3LYP/6-311+G(d,p)], respectively (99UP1).

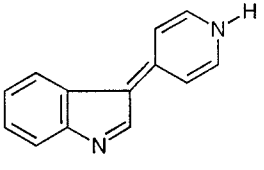
An updated compilation of gas-phase basicities and proton affinities has been published (98MI3).

C. Pyridylindoles and Related Compounds

The tautomerism of pyridylindoles **13, 14** (and related compounds) has been investigated by the pK_a method (72KGS1011).



13



14

For 4-(3-indolyl)pyridine a value of $K_T = 1.99 \cdot 10^{-6}$ was obtained [compare with 2-(3-indolyl)quinoline: $1.32 \cdot 10^{-5}$; 1-(3-indolyl)isoquinoline: $0.89 \cdot 10^{-5}$; 9-(3-indolyl)acridine: $3.80 \cdot 10^{-6}$; 2-(3-indolyl)benzo[*f*]quinoline: $3.16 \cdot 10^{-6}$] (79ZOR2431).

III. Compounds with Potential Hydroxy Groups

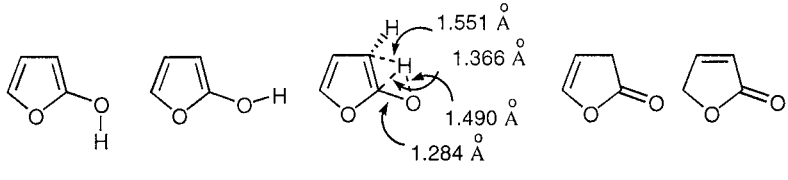
Considerable progress has been made in this area both in synthetic work as well as in computational studies since the last review (76AHCS1, p. 222).

A. Monohydroxyfurans

1. *2-Hydroxyfurans*

2-Hydroxyfuran **15** is tautomeric with 2-oxo-2,5-dihydrofuran **17** [2(5*H*)-furanone, $\Delta^{\alpha,\beta}$-butenolide] and 2-oxo-2,3-dihydrofuran **16** [2(3*H*)-furanone, $\Delta^{\beta,\gamma}$-butenolide] [for reviews on butenolides see (87KGS723; 90H751)]. As already stated in the previous review (76AHCS1, p. 222), the tautomeric forms **16, 17** are far more stable than the hydroxyfuran. DFT studies reveal that there are at least two energy minima of 2-hydroxyfuran (**15a, 15b**) which differ by ca. 1 kcal/mol. The transition state (**TS**) is calculated to be 61.0 kcal/mol higher in energy than **15b** (99UP1). The energies difference between $\Delta^{\beta,\gamma}$-butenolide **16** and $\Delta^{\alpha,\beta}$-butenolide **17** is obtained as 2.9 kcal/mol (Scheme 7) (99UP1).

Experimental investigations have shown that the conjugated keto form is stable (68MI03), but it is possible to prepare the unconjugated keto form (85S786). On standing at room temperature **16** isomerizes to **17** (Scheme 7) with a rate of ca. 3% per month. 2-Hydroxyfuran **15** has never been prepared, and attempts to generate its O-deuterated analog by hydrolysis of the corresponding trimethylsilyl ether even at -45°C yielded only the deuterated 2-oxo-2,3-dihydrofuran **16** (89JA5346). Measurements of ionization potentials for butenolides also clearly exclude an enol form as a major species in the gas phase [75ACS(B)647].



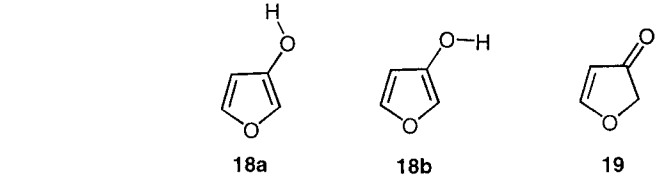
	15a	**15b**	**TS**	**16**	**17**
B3LYP/6-31G*	0.0	+ 1.0	+ 62.0	- 15.0	- 17.9

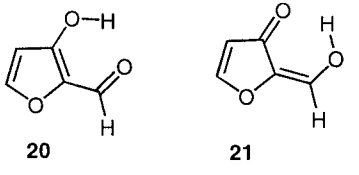
(Relative values in kcal/mol)

Scheme 7

2. *3-Hydroxyfurans*

There are at least two different conformers of 3-hydroxyfuran **18a,b** (Scheme 8). The energy difference is calculated to be 0.4 kcal/mol. According to DFT calculations the keto tautomer **19** is 12 kcal/mol more stable than the 3-hydroxyfuran **18b** (99UP1). If a carbonyl substituent is present

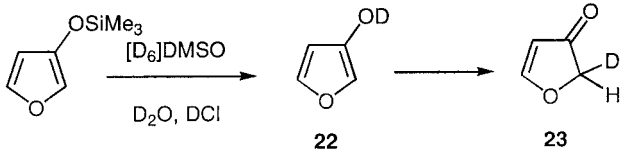




SCHEME 8

at C-2 (e.g., **20**) the hydroxyfuran **20** is more stable than **21** by 4.2 kcal/mol (99UP1). Experimentally it was found that 3-hydroxyfurans exist essentially exclusively in the keto form **19** unless there is a heteroatom containing substituent in position 2 (73RTC731).

A solution which contained ca. 95% of the O-deuterated 3-hydroxyfuran **22** was generated from the trimethylsilyl ether in [D_6]-DMSO/D_2O with DCl at 32°C. After several hours it was converted into the keto tautomer **23** deuterated at position 2 (Scheme 9). In all solvents used (CCl_4, [D_6]DMSO, [D_6]acetone, CD_3OD) no detectable amount of the enol was present at equilibrium (89JA5346).

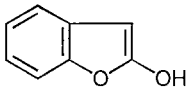


SCHEME 9

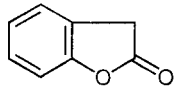
3. *2-Hydroxybenzofurans*

As already summarized earlier (76AHCS1, p. 223), benzofuran-2(3*H*)one [for review see (74HC210)] exists in the carbonyl form **25** with no de-

tectable content of the hydroxy tautomer **24.** This is in accordance with B3LYP/6-31G* calculations (ΔE = 18.4 kcal/mol) (99UP1) (for equilibrium acidities see also 91JOC4218). Murraxonin has been reported to exist as 2-hydroxy-3-methoxybenzo[*b*]furan derivative (87P3319).

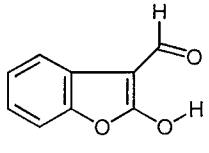


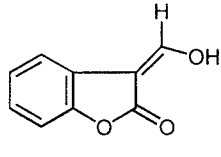
24



25

It was reported that the corresponding 2-hydroxy-3-acetyl-benzofuran exists entirely in the enol form (73AJC1079; 84H737; 87CC1150) [produces deep blue color with ferric chloride (55JA1623)]. This is in accordance with AM1, PM3, and B3LYP/6-31G* calculations for 3-formyl-2-hydroxybenzo[*b*]furan as model compound (99UP1) (see Scheme 10, all values in kcal/mol).

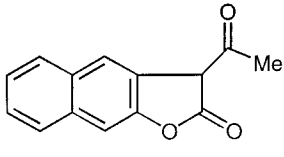


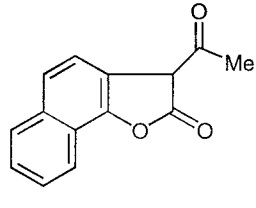


AM1	- 59.3	- 68.8
PM3	- 73.0	- 78.3
DFT (rel.)	+ 5.7	0.0

SCHEME 10

Several 2-hydroxybenzofuran-3-carboxylates have been formulated as keto tautomers [78S66; 79JCS(P1)2382; 93JOC3245]. 3-Acetylnaphtho[1,2-*b*]furan-2-(3*H*)-one and 3-acetylnaphtho[2,3-*b*]furan-2-(3*H*)-one have also been formulated as keto tautomers (Scheme 11) (87CC1150).

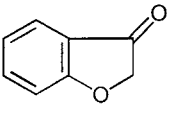




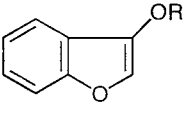
SCHEME 11

4. *3-Hydroxybenzofurans*

3-(2*H*)Benzofuranones (3-coumaranones) (62JOC586) exist exclusively as keto tautomers **26** (ν_{CO} = 1720 cm^{-1}, no OH absorption) (75JHC1051; 88MI3; 89MI5), again in accordance with B3LYP/6-31G* calculations [E (**26**) = −458.90303, E(**27**), (R = H, *Z* rotamer) = −458.88113 (in hartrees), ΔE = 13.7 kcal/mol] (99UP1), although it is possible to generate the hydroxy form *in situ*.



26



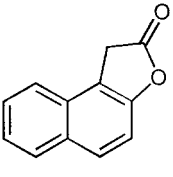
27

R = H, $SiMe_3$

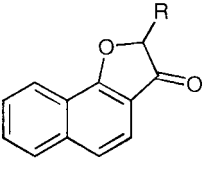
In a solution obtained by hydrolysis of the trimethylsilyl ether (**27,** R = $SiMe_3$, conditions: [D_6]acetone, D_2O, DCl, 5 • 10^{-4} *M*) at 32°C only the enol form was present (**27,** R = D). This solution was stable for several hours at 32°C. Addition of a small amount of HCl leads to [2-^{2}*H*]-3-benzofuranone (89JA5346). Solutions of **27** (R = D) obtained in [D_6]DMSO−D_2O with DCl (1 • 10^{-3} to 1 • 10^{-4} *M*) were stable for 1 day at room temperature (for further references see 86TL3275; 87PAC1577; 88TL250).

Angular annulation of benzo[*b*]furan with a benzene ring leads to naphtho[2,1-*b*]furan and naphtho[1,2-*b*]furan.

Naphtho[2,1-*b*]furan-2-(3*H*)-one **28** has been described as a keto tautomer (91JA2301). Naphtho[1,2-*b*]furan-3-(2*H*)-ones of type **29** (R = H, Me, Et, Pr, pentyl, heptyl) show keto-enol tautomerism with the enol form predominating (88RRC917).

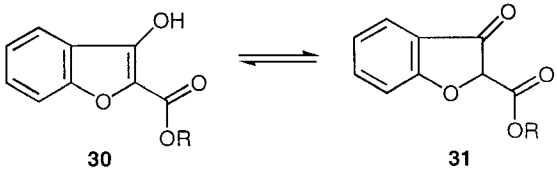


28



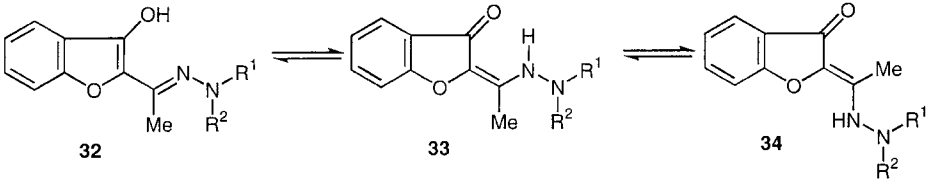
29

As reported earlier (76AHCS1, p. 225), 2-acetyl-3-hydroxyfuran exists as the enol tautomer. 3-Hydroxybenzofurans with an ester group at the 2-position also exist mainly in their hydroxy form **30** with a small amount of the keto isomer **31** (48CB203; 75AP272).



30 **31**

Hydrazones of 3-hydroxy-2-acetylbenzo[*b*]furan are reported to exist as aminovinylketones **33** and **34** (90ZOR1540). The ratio of (*Z, E*) isomers depends upon R^1 and R^2.



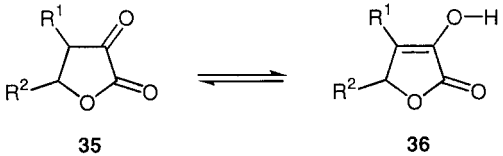
32 **33** **34**

Irradiation at the long-wavelength maximum causes a significant alteration of the UV spectrum with the appearance of new bands, which correspond in their position to a hydroxyhydrazone isomer **32.**

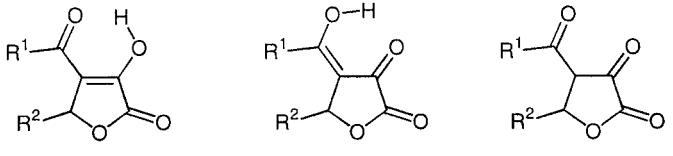
B. Potential Dihydroxyfurans

1. *Oxygen Functions in 2,3-Positions*

Since the last review (76AHCS1, p. 226), much work has been done in the area of 2,3-dihydroxyfurans. Compounds of this type (α-keto-γ-butyrolactones) exist in two tautomeric forms **35** and **36.**



35 **36**



37 **38** **39**

Whereas the parent compound [R^1 = R^2 = H; α-tetronic acid (15JCS1254; 95MI2)] was reported to exist as enol **36** (97CC571), its derivatives (R^1 = H, R^2 = alkyl; R^1 = R^2 = alkyl) may exist as enol tautomers (12CB3702; 48HCA473; 50HCA130; 63T483; 73CC499; 74JOC2013; 76CB3115; 78JHC693, 78TL1557; 83JOC5017; 87HCA369; 88BCJ4427, 88JOC2769; 91CL1349; 92JOC4558; 95MI2; 96T12723; 97JPR20) or as mixtures of both hydroxy and oxo tautomers (81CC1139; 86JPR682; 89T6631; 94JA10403). Computational results reveal that the calculated energy difference depends critically upon the basis set used for calculation [for the parent compound (**35, 36;** R^1 = R^2 = H), see Table V].

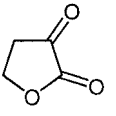
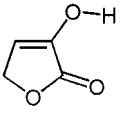
In cases where R^1 = aryl, hetaryl, R^2 = H (and others) α-keto-γ-butyrolactones seem to exist entirely as enol tautomers [81JCS(P1)1969, 81TL1591; 82G1; 85CC340; 86TL2015; 92JOC4558].

There are three tautomeric 4-acyl-α-keto-γ-butyrolactones **37–39.** All studies done on compounds of this type have shown that they exist practically exclusively as enols **37** (68YZ919; 78JHC737, 78YZ802; 80OMR516; 82JOC1200; 83CPB912, 83JHC289, 83JHC359; 86JHC199; 88TL1763; 91JHC1501, 91TA415; 93JHC161; 98JHC25). This is again in accordance with DFT studies (for R^1 = R^2 = H) [E(**37**) = –493.81110, –493.96455; E(**39**) = –493.80077, –493.95073 (values in hartrees), B3LYP/6-31G* and B3LYP/6-311++G(d, p), respectively] (99UP1) (for further references see 76BSF167, 76BSF1541; 77CPB2593; 80IZV394, 80JOU689, 80MI2; 81MI2; 85JOU2398; 88CPB1404; 89MI6; 98MI2). A general review on α-keto-γ-butyrolactones has been published (94MI2).

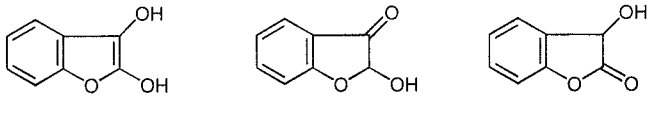
2,3-Dihydroxybenzo[*b*]furan **40** is unknown in the dihydroxy form. According to DFT studies (99UP1), this compound is less stable than the corresponding tautomers **41** and **42** (Scheme 12). Compounds of these types have been reported occasionally [78JOC1541; 79BSF(2)583; 80IJC(B)104; 83JPR382; 89P235].

TABLE V

CALCULATED ENERGIES FOR α-TETRONIC ACID (B3LYP/BASIS)[a] (99UP1)

Method (basis)			ΔE^b
6-31G*	−380.48772	−380.48502	−1.7
6-311++G(d, p)	−380.60345	−380.60749	+2.5
6-311G(3df, 3pd)//6-311++G(d, p)	−380.62336	−380.62947	+3.8

[a] Values in hartrees.
[b] Values in kcal/mol



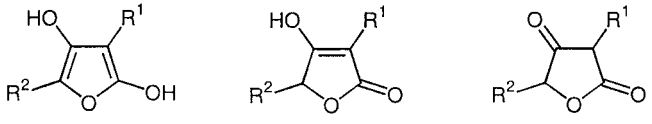
	40	41	42
B3LYP/6-31G*	- 534.09629 (17.0)	- 534.11587 (4.7)	- 534.12337 (0.0)

SCHEME 12. Values in hartees (relative values in parenthesis and in kcal/mol).

Coumaran-2,3-semidione was prepared by treatment of coumaran-2,3-dione with the enolate anion of propiophenone in DMSO (70JA2762).

2. *Oxygen Functions in 2,4-Positions*

As it is well known, 2,4-dihydroxyfurans **43** (tetronic acids) exist as equilibrium mixtures of keto-enol **44** and dioxo forms **45.**

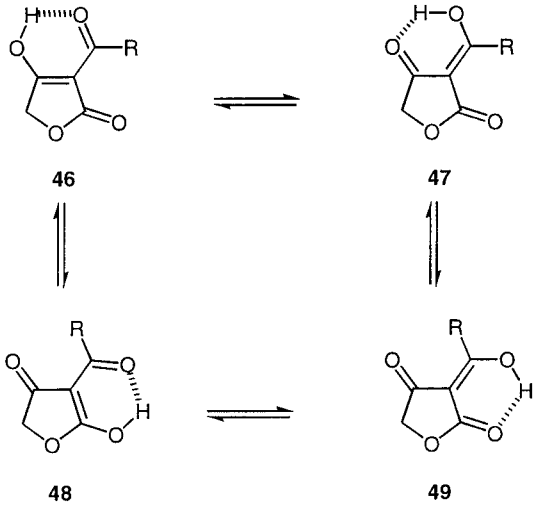


43 **44** **45**

It has been stated that tetronic acids substituted at C-3 by hydrogen or by alkyl groups exist almost exclusively as keto-enols [81JCS(P1)1173; 84SA(A)1007]. There are several reports concerning reactions of tetronic acids [1896CB1042; 50JOC572; 73T4251; 75JCS(P1)635; 79T2181; 81CJC1722, 81JHC719; 85JOC5233; 87TL1039; 92JOU1295; 97MI5], but quantitative data for these equilibria are scarce. According to the vibrational assignment of tetronic acid (IR and FT-Raman spectra of both deuterated and undeuterated material) the enol form **44** predominates in the solid state, although some keto form **45** is also observable (93JST35).

A keto-enol equilibrium was reported for 5-(2-bromoethyl)tetronic acid (according to ^{13}C NMR in $CDCl_3$) (94T8237). 5-Methyltetronic acid exists as a keto-enol mixture in $CDCl_3$ (^1H and ^{13}C NMR), whereas in [D_6]DMSO only the enol form is present (84JOC927). 3-Nitrotetronic acids ($R^1 = NO_2$; $R^2 = H, Me$) have been shown to exist as enols [84SA(A)1007]. MNDO calculations (for the gas phase) are at variance with these results (87MI2), but it has been stated that solvent effects may be responsible for these discrepancies.

Tautomeric equilibria of 3-acyltetronic acids are more complex. Without taking a triketo tautomer and $\Delta^{4,5}$ isomers into consideration, there are four



46 **47**

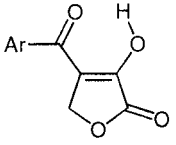
48 **49**

different forms with a rapid equilibrium of **46** ⇌ **47** and **48** ⇌ **49** and a slow equilibrium of **46** ⇌ **48, 47** ⇌ **49.**

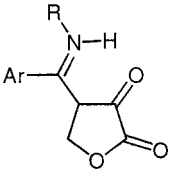
For the simplest case (3-formyltetronic acid, R = H) these equilibria have been investigated by NMR spectroscopy. It was found (81JHC663) that only **46** and **47** are present in the ratio **46/47** = 68/32 in $CDCl_3$ [for MNDO results see (86MI3; 87MI2)]. AM1 and *ab initio* calculations (3-21G) have also been reported for 3-formyltetronic acid (95IZV1043). For 3-acetyltetronic acid (R = Me) there is an equilibrium between **46/47** and **48/49** with a preference of the two former tautomers (in ratio 60/40 in $CDCl_3$). Tautomers **46** and **47** are either in a rapid equilibrium (**46/47** = 1/1) or exist as a symmetrical structure (80TL4491). For earlier investigations see [76BCJ1161, 76JHC533, 76MI1; 77ACS(B)756, 77MI1, 77MI2; 78BCJ651; 79JCS(P2)1605]. Both AM1 and PM3 calculations are reported to be in satisfactory agreement with experimental data (90MI4). The vibrational spectra of 3-acetyltetronic acid were investigated in different aggregation states (95IZV1043). For further studies on 3-acyltetronic acids see [88LA355; 90DOK1381; 94JCS(P1)2513; 95IZV1043; 97SL909; 98JCS(P1) 411]. Antibiotics with a 3-acyltetronic acid structure have been isolated and investigated by X-ray spectroscopy (81CC1073; 91T8285).

The synthesis of a selenonium ylide with a tetronic acid anion moiety was reported (83TL75; 84CPB2666). 3-Enamino-tetronic acids have also been investigated (82SC431).

As has been pointed out previously, 4-aroyl-3-hydroxy-2(5*H*)furanones **50** are enolic. The corresponding imine exists as the tautomeric dicarbonyl structure **51** (93JHC161) (Schemes III and IV of this reference contain printing errors). For more information see also (91JHC1501).



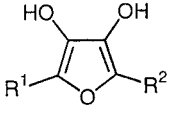
50



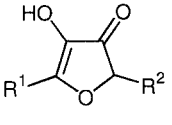
51

3. *Oxygen Functions in 3,4-Positions*

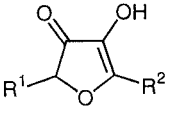
Although in the earlier literature a number of 3,4-dihydroxyfurans (**52,** R^1, R^2 = acyl) have been reported, 2,5-dialkyl-3,4-dihydroxyfurans (**52,** R^1, R^2 = alkyl) exist as hydroxyfuranones **53** or **54** [73HCA1882; 74RTC312, 74YZ1139; 81S709; 83JOC3493, 83MI4; 85JCS(P1)795; 87S377; 89JCS(P1) 133, 89P631; 91T9351; 92JOC5023; 94BCJ2891; 96TL2955; 97JHC533, 97MI9] with no indication of a tautomeric equilibrium between **52** and **53.** Quantum chemical studies are in accordance with these observations (see Table VI).



52



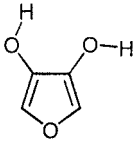
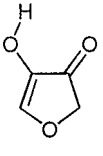
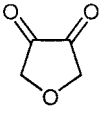
53



54

TABLE VI

DFT RESULTS FOR 3,4-DIHYDROXYFURAN **55** AND THE CORRESPONDING TAUTOMERS[a] (99UP1)

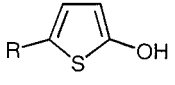
Method (basis)	Energies[b]		
	 **55**		
6-31G*	−380.43663	−380.45872	−380.45133
6-311++G(d, p)	−380.56651	−380.58227	−380.56865
6-311G(3df, 3pd)//6-311++G(d, p)	−380.59549	−380.61016	−380.59526

[a] B3LYP functional.
[b] Values in hartrees.

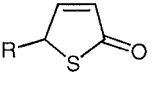
C. Monohydroxythiophenes and -Selenophenes

1. *2-Hydroxythiophenes*

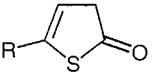
2-Hydroxythiophenes **56** have two possible keto tautomers (**57** and **58**) [for review see (86HC1)]. As has been pointed out earlier (76AHCS1, p. 229), the tautomerism of 5-substituted compounds was extensively studied by Lawesson and coworkers (63T1867) and by Hörnfeldt (63MI1; 68MI1). For 5-alkyl compounds, only the keto forms were present, whereas with R = phenyl, thienyl and ethoxycarbonyl substantial amounts of the enol forms were detected. Computations for the parent system (R = H) showed that the $\Delta^{\alpha,\beta}$-thiobutenolide of type **57** is most stable (Table VII).



56



57



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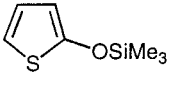

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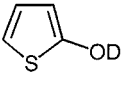

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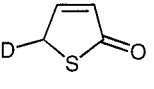

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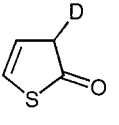
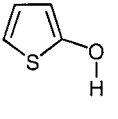
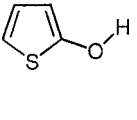
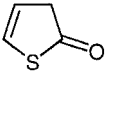
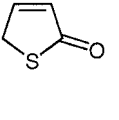


62

The unsubstituted 2-hydroxythiophene **56** (R = H) exists (as the neat liquid) as 3-thiolen-2-one (**57,** R = H) (60MI1; 74JHC291). Hydrolysis of 2-[(trimethylsilyl)oxy]thiophene **59** in [D_6]DMSO-D_2O at 32°C immediately

TABLE VII

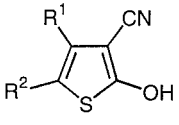
DFT Results for 2-Hydroxythiophene and the Corresponding Keto Tautomers[a] (99UP1)

Method (basis)	Energies[b]			
				
6-31G*	–628.20888	–628.20995	–628.22826	–628.23500

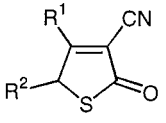
[a] B3LYP functional.

[b] Values in hartrees.

gave 2-deuterooxythiophene **60.** After about 10 min this compound converted into a mixture of [5-$^2H_1$]-3-thiolene-2-one **61** (65%) and [3-$^2H_1$]-4-thiolene-2-one **62.** The 4-thiolene-2-one was unstable and after 45 min it was converted to 3-thiolen-2-one (86TL3275; 87PAC1577; 88TL250; 89JA5346). For more work on 2-hydroxythiophenes see [75ACS(B)647].



63



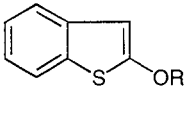
64

	R^1	R^2
a:	Ph	H
b:	Me	H
c:	Me	CO_2Et
d:	Me	CO_2Me

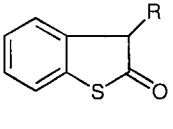
According to the IR spectra (neat), nitriles **63a,b** exist as 3-thiolene-2-ones **64a,b.** For R^1 = Ph, R^2 = H, in $CDCl_3$ solution only the keto tautomer **64a** was found; however, addition of [D_6]DMSO shifts the equilibrium toward **63a.** In pure [D_6]DMSO there is a mixture of **63a:64a** = 1:1. Nitrile **63c** exists exclusively as hydroxy tautomer [compare with ethyl-2-hydroxythiophene-5-carboxylate (63T1867)] as does **63d** (75JPR861).

2. *2-Hydroxybenzothiophenes*

As it is well known (76AHCS1, p. 232), 2-hydroxybenzothiophene (**65,** R = H) exists both in the solid state and in solution exclusively as its keto tautomer (**66,** R = H). According to DFT calculations, tautomer **66** is more stable than **65** by ΔE = 15.0 kcal/mol [E(**65**) = −781.86390; E(**66**) = –781.88775 (B3LYP/6-31G*, in hartrees)] (99UP1). The 2-hydroxybenzothiophene (**65,** R = D) was generated from the *O*-trimethylsilyl derivative (**65,** R = TMS) in [D_6]-DMSO-D_2O (9:1 v/v)-DCl (10^{-4} M) at −34°C. After 15 min at −25°C the spectra had changed to that of [3-$^2H_1$]-2-benzothiophenone **66** (R = D) (89JA5346).

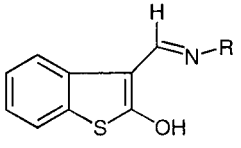


65

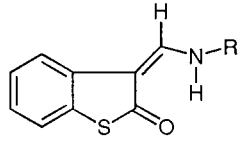


66

2-Hydroxybenzothiophenes with carbonyl groups at C-3 (e.g., COCH=CHPh) have been formulated as enols (79LA965; 81CC118). In some cases mixtures of enol and oxo forms have been observed (84CCC603). Aldimines of type **67** exist predominantly as keto tautomers **68** (74JPR971).



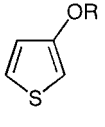
67



68

3. *3-Hydroxythiophenes*

The tautomeric equilibrium of 3-hydroxy-2-methylthiophene has been reported previously (76AHCS1, p. 233). 3-Hydroxythiophene **69** (R = H), an unstable liquid, was shown by infrared spectroscopy to exist as a mixture of **69** (R = H) and **70** in the pure liquid state (56JCS4985). The enol content in several solvents was determined by ^{1}H NMR spectroscopy ([D_6]-DMSO: 100%, [D_6]-acetone: 100%, MeOH: 100%, dioxane/water (9:1): ~ 95%, CCl_4: ~ 65%; for CCl_4 solution see also [86TL5155; 89JA5346 (footnote 33)]). Deuterooxythiophene (**69,** R = D) could also be generated from its *O*-trimethylsilyl derivative **69** (R = TMS) in [D_6]-acetone−D_2O (4:1 v/v)-DCl (10^{-3} *M*) as unstable compound (89JA5346).



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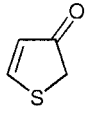


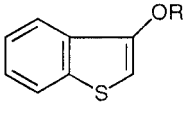
70

2-(2-, 3-, and 4-Pyridyl)-3-hydroxythiophenes have been shown by ^{1}H NMR spectroscopy and IR measurements to exist exclusively as enols (92ACS654). 3-Hydroxythiophene-2-carboxylates have been formulated as hydroxy tautomers (91JMC2186) [for further work on hydroxythiophenes see 75ACS(B)652; 76BSF265; 90CC375; 92JCS(P2)935].

4. *3-Hydroxybenzothiophenes*

In the earlier literature there were conflicting reports whether 3-hydroxybenzothiophene **71** (R = H) or its keto tautomer **72** is more stable. Later, this equilibrium was investigated in detail (76AHCS1, p. 235). The

solid material obtained by standard methods [e.g., (74CS184)] was the keto tautomer (89JA5346). In [D_6]DMSO after about 1 day the equilibrium mixture contains 87% enol **71** (R = H). In $CDCl_3$ only the keto form **72** is present (unchanged over 2.5 years) as already reported by Stridsberg and Allenmark (74CS184). For a (qualitative) observation of a keto-enol tautomerization in a substituted benzo[*b*]thiophene see (99H259).



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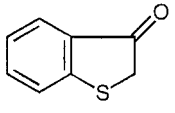
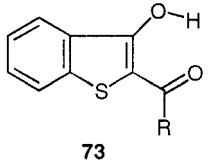


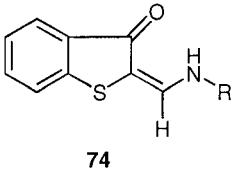
72

3-Hydroxybenzo[*b*]thiophene could be generated in 100% as enol (**71,** R = D) by hydrolysis of its *O*-trimethylsilyl derivative (**71,** R = TMS) (conditions: 90% [D_6]DMSO, 10% D_2O; with $5 \cdot 10^{-4}$ *M* DCl). Under these conditions (32°C) the enol **71** has a half-life of about 1 day and converts slowly to give an equilibrium mixture containing 40% of the keto form (89JA5346). 3-Hydroxy-4-methoxythiophene has been formulated as the enol (96JPR672). 2-Acyl-3-hydroxybenzo[*b*]thiophenes (**73,** R = OMe, OEt) and the corresponding amides (**73,** R = NH_2, NHPh) were reported to exist as hydroxy tautomers (75AP272).



73

The spectra of aldimines **74** and X-ray investigations on hydrazones of type **75** demonstrate the existence of these compounds in the corresponding keto forms (74JPR971; 92IZV917).



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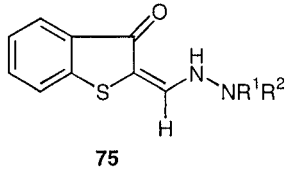
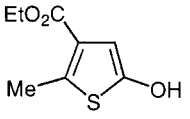
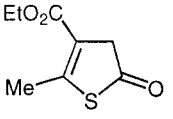


75

^{1}H NMR spectra of thiophene **77** indicate a small amount (8.4% in CS_2) of the second keto tautomer **78.** The enol tautomer **76** could not be detected [78JCS(P1)292].



76



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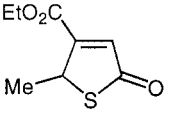
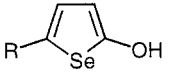


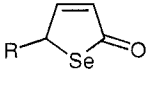
78

5. *2-Hydroxyselenophenes*

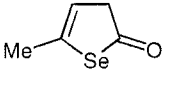
Both unsubstituted 2-hydroxyselenophene **79** (R = H) as well as the 5-methyl derivative **79** (R = Me) exist mainly as 3-selenolene-2-ones **80.** For compound **79** (R = Me) it was possible to isolate **81** and study its tautomeric isomerization. In benzene there is an equilibrium mixture of **80** (R = Me) (93%) and **81** (7%).



79



80

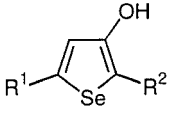


81

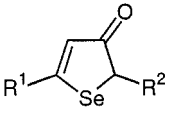
Equilibrium constants and activation parameters have been determined [76ACS(B)101] [for a review see 82AHC(30)127]. Ionization potentials for tautomeric 2-hydroxyselenophenes have been analyzed by comparison with IP data for compounds derived from either tautomeric form. The enol form could not be detected [75ACS(B)647].

6. *3-Hydroxyselenophenes*

2,5-Dialkyl-3-hydroxyselenophenes exist in a keto-enol equilibrium **82** ⇌ **83** (72CS9). Analysis of the ionization potentials showed that for these compounds both the keto and the enol form are important [75ACS(B)652].



82

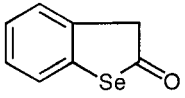


83

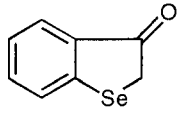
2-Formyl- and 2-acetyl-3-hydroxyselenophenes have been formulated as enol tautomers (72JHC355).

7. *2- and 3-Hydroxybenzoselenophenes*

According to spectra (IR: $\nu_{C=O} = 1735\ cm^{-1}$, in CCl_4; ^1H and ^{13}C NMR), 2-hydroxybenzoselenophene exists as keto tautomer **84** [76JCS(P1) 2452] (for further references see 88T6119; 89JOC240).



84



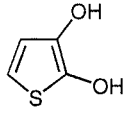
85

The corresponding 3-oxo derivative **85** also exists as the keto tautomer [12CB1835; 75BSF783, 75CS29; 76JHC469; 83JHC49, 83SA(A)693; 85IZV861]. 3-Hydroxy-2-phenylbenzo[*b*]selenophene has been formulated as enol tautomer (93TL2875). For further work on 3-hydroxybenzo[*b*] selenophenes see [78BSF(2)241]. For keto-amine tautomerism in 2-aminoalkylidenebenzo[*b*]selenophenes see (75KGS781). ^{77}Se NMR spectra of 3-acyl-2-hydroxybenzo[*b*]selenophenes have been reported (81OMR14).

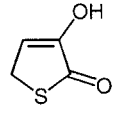
D. Potential Dihydroxythiophenes

1. *Oxygen Functions in the 2,3- and 2,4-Positions*

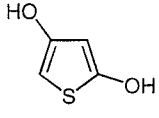
Unsubstituted 2,3-dihydroxythiophene **86** (71T3839) prefers the mono-keto-mono-enol form **87** both for solid and liquid state and for EtOH and $CDCl_3$ solution (76AHCS1, p. 237). As has been pointed out previously (76AHCS1, p. 238), many 2,4-dihydroxythiophenes **88** were shown to exist as thiotetronic acids **89** (13CB2103; 71T3839).



86



87



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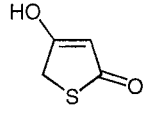
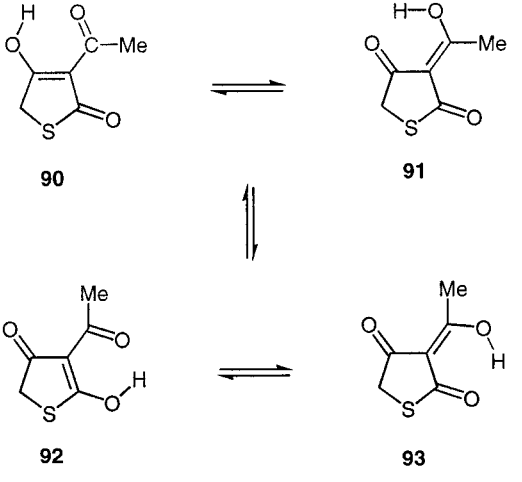


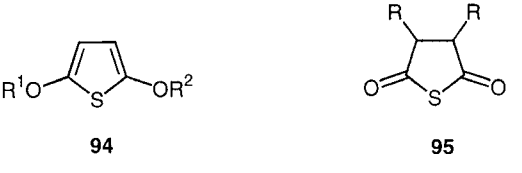
89

For 3-acetylthiotetronic acid the same type of tautomerization process (**90** ⇌ **91, 92** ⇌ **93** as a result of prototropy between "internal" tautomers; **90, 91** ⇌ **92, 93,** rotation of the side-chain group, between "external" tautomers) was observed as for the corresponding 3-acetyltetronic acids (^{1}H NMR, ^{13}C NMR) [76JHC533; 78BCJ651; 79JCS (P2)1605].



2. *Oxygen Functions in the 2,5-Positions*

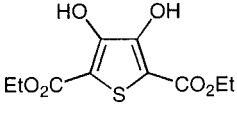
2,5-Dihydroxythiophene **94** ($R^1 = R^2 = H$) exists in the dioxo tautomeric form (thiosuccinic anhydride, **95;** R = H) (76AHCS1, p. 239). Deuterated 2,5-dihydroxythiophene **94** ($R^1 = R^2 = D$) was detected during hydrolysis ([D_6]DMSO−D_2O, small amount of DCl, 30°C) of 2,5-bis [(trimethylsilyl)oxy]thiophene **94** ($R^1 = R^2 = TMS$).



First, the monodeuterated thiophene **94** ($R^1 = TMS$, $R^2 = D$) was observed, which was further hydrolyzed to **94** ($R^1 = R^2 = D$). The latter is converted into deuterated thiosuccinic anhydride **95** (R = D) after 1 h (89JOC1211).

3. *Oxygen Functions in 3,4-Positions*

Mono saponification of diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate **96** (67T2437) (1 *N* NaOH, then HCl) results in the formation of **97** (28%) as a white solid. According to ^{1}H, ^{13}C, and X-ray data, this compound is a true 3,4-dihydroxythiophene. Two lines of evidence have been reported that a less stable keto tautomer may be accessible from (or in equilibrium with) **97.** First, C-5 hydrogen of **97** is readily exchanged for deuterium with NaOD-D_2O. Second, acid-catalyzed hydrolysis of **96** in a water–ethanol mixture yields not only **97** (37%), but also monoethyl ether **98** (20%). The formation of **98** may be the result of reaction between ethanol and a low equilibrium concentration of **99** (93TL8229).



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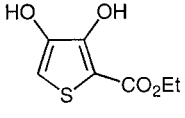

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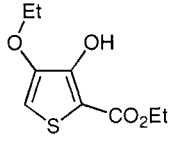

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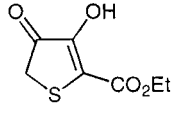
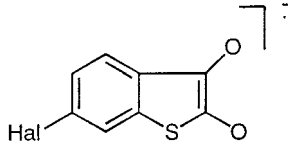


99

2,5-Diacyl-3,4-dihydroxythiophenes have been formulated as dienol tautomers (77T191). The same holds for 2,5-diaryl- and 5-aryl-2-carboxy derivatives (91JHC1449). ESR investigations of 6-halogeno-benzo[*b*] thiophene-2,3-semidiones (Scheme 13) have been reported (81JOC751).

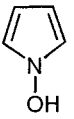
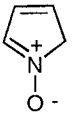
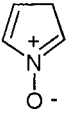


SCHEME 13

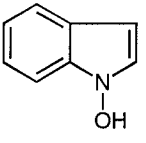
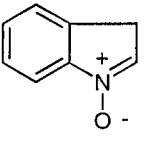
E. MONOHYDROXYPYRROLES AND -INDOLES

1. *N-Hydroxypyrroles*

Since the appearance of the last review (76AHCS1, p. 239), there has been considerable progress in the investigation of *N*-hydroxypyrroles (88JOC2268; 95JOC4302). These compounds can exist in three tautomeric forms (Scheme 14). In all cases reported up to now, the simple derivatives exist entirely in the *N*-hydroxy form. Nitrone tautomers do not seem to have been observed [84LA199; 86JCR(M)2701, 86JCR(S)318; 88JOC2268;

B3LYP/6-31G* (6-311+G(d,p), rel. values in kcal/mol)	0.0 (0.0)	4.8 (8.4)	8.5 (11.9)

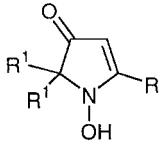



0.0 (0.0) 5.0 (4.8)

SCHEME 14

95JOC4302; 98JOC9131]. This is in accord with quantum chemical calculations. A DFT treatment (B3LYP/basis set) shows that nitrone tautomers of *N*-hydroxypyrrole (and *N*-hydroxyindole) are less stable than the hydroxy tautomers (Scheme 14) (99UP1). An X-ray structure determination of a *N*-hydroxypyrrole derivative has been reported (88JOC2268). For further work on *N*-hydroxypyrroles see (92MI3 and 95ZOR1502).

N-Hydroxy-pyrroles of type **100** are in a tautomeric equilibrium with the corresponding nitrones **101.**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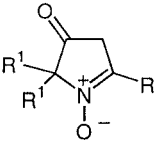
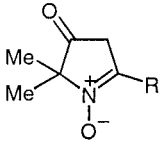
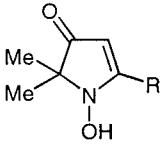

101

For the parent compounds (R = R^1 = H), the AM1 method (ΔH_f^0 (**100**) = −11.58 kcal/mol; ΔH_f^0 (**101**) = −6.76 kcal/mol) fails to predict correct energies. However, PM3 (ΔH_f^0 (**100**) = −24.54 kcal/mol; ΔH_f^0 (**101**) = −24.73 kcal/mol) and MINDO/3 calculations (ΔH_f^0 (**100**) = −30.10 kcal/mol; ΔH_f^0 (**101**) = −32.72 kcal/mol) indicate that these tautomers are

of similar stability (99UP1). DFT calculations [B3LYP/6–311+G(d,p)] gave similar results [E(**100**) = –360.66309, E(**101**) = –360.65849; in hartrees (for R = R^1 = H)] (99UP1). This is in accordance with experimental observations. This equilibrium depends both on the substitution and on the solvent (see Scheme 15) (90IZV395, 90KGS921; 91IZV437). For further work see 80JOC4998.



102



103

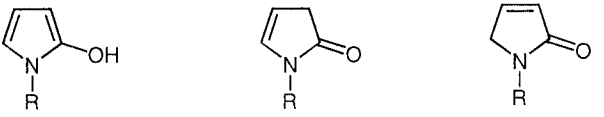
R:	**102/103** [D_6]DMSO	**102/103** $CDCl_3$
Me:	0/100	40/60
Ph:	15/85	93/7
CF_3:	0/100	-
2-pyridyl:	50/50	100/0

SCHEME 15

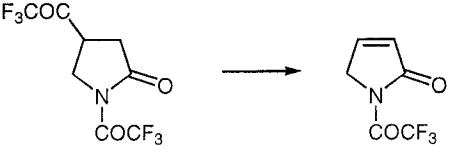
2. *2-Hydroxypyrroles*

2-Hydroxypyrrole **104** exists as keto tautomers **105** and **106** (Scheme 16). According to B3LYP/6-31G* calculations (and in line with experimental observations, see below), **104** is far less stable than **105** and **106,** which are of nearly equal stability (Scheme 16) (99UP1). Earlier investigations (76AHCS1, p.241) have shown that there may be a slight preference of the Δ^4 form **105** to the Δ^3 alternative **106.** The synthesis of **108** was accomplished by treatment of **107** with Et_3N. Treatment of **108** with $KHCO_3$ in $MeOH/CH_2Cl_2$ yields a mixture of **106** (R = H) and **105** (R = H) in a ratio of 8:1. After equilibration the mixture contains **106** and **105** in a ratio of 9:1.

Compound **106** (R = H) was obtained in almost pure form (≤ 0.5% **105**) by crystallization. Compound **105** (R = H) was obtained by chromatography with 84% purity. The preparation of a mixture of **106** and **105** (R = Me) was also reported. Compound **106** (R = Me) could be enriched [up to 98% with 2% **105** (R = Me)] by crystallization (79JOC2798). AM1, PM3, and MINDO/3 calculations all fail to predict the correct energies [for R = H: ΔH_f^0 (**104**) = 1.13, –3.04, –29.75 kcal/mol; ΔH_f^0 (**105**) = –12.88, –24.04,



	104	**105**	**106**
DFT (rel., kcal/mol) (for R = H)	18.3	0.8	0.0

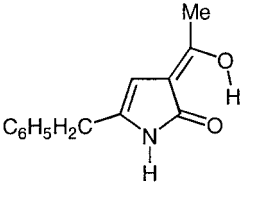


107 **108**

SCHEME 16

–36.93 kcal/mol; ΔH_f^0 (**106**) = –6.22, –18.15, –33.45 kcal/mol (AM1, PM3, MINDO/3)] [77LA565; 83JCR(S)284; 87JHC457; 99UP1]. For HMO calculations see (79MI1).

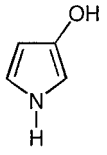
For 3-acetyl-5-benzylpyrrolin-2-one, the keto-enol tautomer **109** predominates according to spectral data (UV, IR, ^{1}H and ^{13}C NMR) (80HCA121) (for further work on pyrrolin-2-ones see 77JHC681; 95MI1).



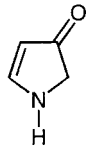
109

3. *3-Hydroxypyrroles*

Since the last review (76AHCS1, p. 243), progress has been made both in the synthesis as well as in tautomerization studies of 3-hydroxypyrroles (for a review see 92HC525). The parent compound can exist in at least two tautomeric forms (**110** and **111**). According to MINDO/3 and PM3 calculations (79JOC374; 99UP1) **110** is more stable than **111** [$\Delta\Delta H_f$ =2.3 kcal/mol (PM3)].

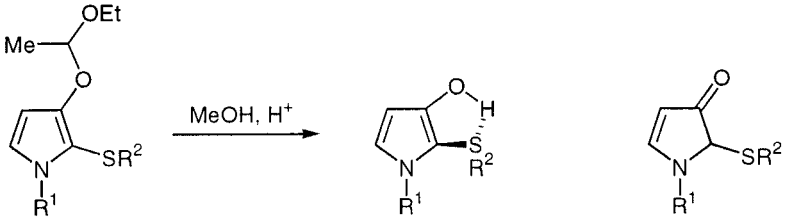


110



111

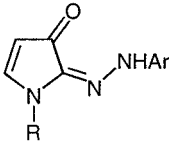
AM1 calculations give a different stability order ($\Delta\Delta H_f = -2.3$ kcal/mol). It was remarked that because of the high dipole moment of **111** (μ = 5.197 D) compared to **110** (μ = 2.899 D) (MINDO/3 values) a solvent could strongly effect an equilibrium between **110** and **111** (79JOC374). DFT calculations (B3LYP/6-31G*) indicate that the keto tautomer **111** is more stable than **110** by 7.4 kcal/mol (99UP1). Using ^{1}H NMR spectroscopy, Momose and coworkers showed that 1-methyl, 1-benzyl, and 1-phenyl derivatives of 3-hydroxypyrrole exist as the keto tautomers in $CDCl_3$ solution (79CPB1448). McNab and Monahan prepared the 1-*tert*-butyl and 1-phenyl compounds and confirmed that these compounds exist as keto tautomers in $CDCl_3$ solution. In [D_6]DMSO solution the enol forms predominate to an extent of 85–95% (85CC213) (for effects of other solvents see [88JCS(P2)1455]). Methanolysis of 3-(trimethylsilyloxy)pyrrole yielded an unstable oil which resinified very rapidly. When it was dissolved in [D_6]DMSO, it initially gave the ^{1}H NMR signals of the 3-hydroxypyrrole. A solution of 3-hydroxy-1-methylpyrrole was prepared similarly (89JA5346). For further work on 3-hydroxypyrroles [1*H*-pyrrole-3(2*H*)-ones] see 88JCS(P2)1459, 89JCS(P1)419, 91JCR(S)316 (^{1}H NMR and ^{13}C NMR spectra), 88JCS(P2)1463 (protonation studies), 88JCS(P2)759, 91JCS(P2) 1999 (^{1}H NMR and ^{13}C NMR spectra), 91JCS(P1)3245 (allylation reactions), and 76LA383 (synthesis). Recent work by Trofimov *et al.* (99UP2, 99DISS1) offers an access to a new family of 3-hydroxypyrroles. Deprotection of **112** with a trace of hydrochloric acid in methanol releases 3-hydroxypyrrole **113** in 85% yield. Unlike most 3-hydroxypyrroles reported in the literature as highly unstable compounds, 1-alkyl-2-(alkylthio)-3-hydroxypyrroles turned out to be quite stable. At high dilution in tetrachloromethane one major hydroxy band at 3534 cm^{-1} (for $R^1 = R^2$ = Me) was observed, indicating a strong intramolecular hydrogen bonding between the hydroxyl and the alkylthio group. ^{1}H and ^{13}C NMR reveal that in $CDCl_3$ the pyrroline tautomer **114** is present in an extent of approximately 10% (for $R^1 = R^2$ = Me).



112 **113** **114**

R^1= alkyl, Ar; R^2=alkyl

Diazo-coupling products of 1-substituted 1*H*-pyrrol-3(2*H*)-ones have been shown by X-ray crystallography to adopt the hydrazone structure **115** [91JCS(P1)701].



115

R = Me, Ph, ^{t}Bu

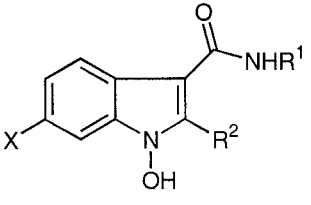
N-Acylated 3-hydroxypyrroles prefer the oxo form (87TL4395; 90LA 397). Compounds of type **116** [5-(2-acylhydrazino)-4-ethoxycarbonyl)-2-oxo-2*H*-pyrrole-3-acetate] are in a tautomeric equilibrium with the corresponding acylhydrazones **117** (95H1479).

116 **117**

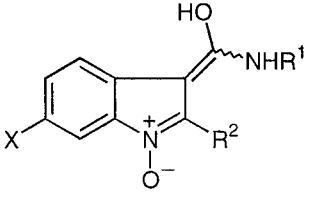
4. *N-Hydroxyindoles*

Since the last review (76AHCS1, p. 240), progress has been made in the synthesis of *N*-hydroxyindoles (83JOC3639; 94C4991; 97T5501). Com-

pounds of this type have also been observed in the Leimgruber–Batcho indole synthesis (85JHC121; see also 81CPB726). As was pointed out earlier the equilibrium between the *N*-hydroxy form and the corresponding nitrone strongly depends on the solvent. Whereas compounds of type **118** in the solid state entirely exist as nitrones **119** (80TL281), in solution ($CDCl_3$, [D_6]DMSO) no nitrone could be detected (83JOC3639). NMR spectra of other *N*-hydroxyindoles seem to indicate that in solution only the hydroxy form is present (86CPB4116; 87JOC1417; 90S801; 92AP433, 92H2269, 92JOC6508; 98H1117; 99H1157). An X-ray structure determination of a *N*-hydroxyindole complex has been reported (83G1530; see also 90M165) (see also Scheme 14).



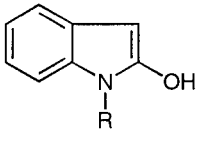
118



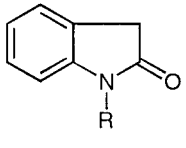
119

5. *2- and 3-Hydroxyindoles*

The tautomerism of hydroxyindoles (and mercaptoindoles) has been reviewed (79HC1). As was pointed out previously (76AHCS1, p. 243) 2-hydroxyindoles **120** exist as lactams **121** (indolin-2-ones). The same holds for the corresponding *N*-hydroxy derivatives (1-hydroxyoxindoles) **121** (R = OH) (86AP1084, 86JOC1704; 90SC2133; 94MI4).

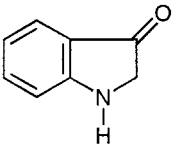


120

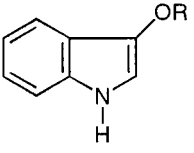


121

Indoxyl **122** (prepared from the corresponding *O*,*N*-diacetate) exists in the solid state as keto tautomer (as confirmed by IR spectrum) (65CC381). Analysis of its solution in [D_6]DMSO showed the presence only of the keto form **122** which, over a period of 24 h, converts to the enol **123** (R = H) (>90%).



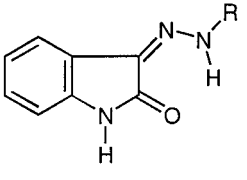
122



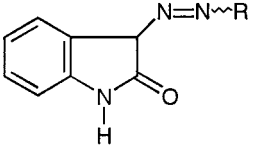
123

The O,N-dideuterated enol was formed by hydrolysis of the O-trimethylsilyl ether **123** (R = TMS) (in 80% [D_6]DMSO/20% D_2O with $5 \cdot 10^{-4}$ *M* DCl). *N*-Methylindoxyl (formed by hydrolysis of its acetate) exists in the solid state as a mixture of the enol and the keto tautomers (34% enol/66% keto). The NMR spectrum of freshly prepared solution in DMSO demonstrated signals of both enol and keto forms. However, at equilibrium (reached in 18 h at RT) the ratio of enol to ketone depends strongly on the polarity of the solvent used: thus, in [D_6]DMSO the tautomeric mixture contains 92% enol, while in $CDCl_3$ the keto form predominates (97%). A solution with 100% enol could be generated by hydrolysis of its O-trimethylsilyl ether [conditions: 80% [D_6]DMSO/20% D_2O with $5 \cdot 10^{-4}$ *M* DCl at 32°C (86TL3275; 87PAC1577; 88TL250)].

Monosubstituted hydrazones of isatin can exist in at least three tautomeric forms **124–126.** According to spectroscopic data, only hydrazone **124** is present in solution (81JOC2764).



124



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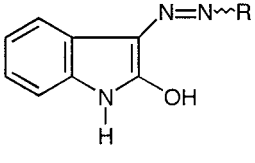
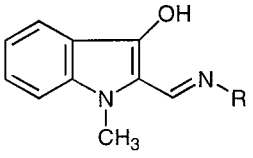


126

Preliminary studies with a thio derivative of isatin (indole-2-thione-3-phenylhydrazone) also showed the hydrazone structure to be the favored tautomeric form (81JOC2764).

Phenylmercury derivatives of 3-aminomethylene-1-methyloxindols have also been investigated (79KGS65). For studies of the effect of substituents on the electronic structure of silver and potassium salts of 3-(aryl)iminooxindole see 76MI2. The keto-enol and imino-enamine tautomerism of compounds of type **127** (with **128** and **129**) has been investigated (85KGS921).



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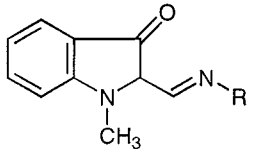
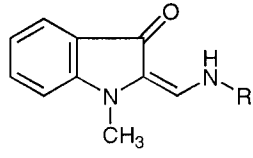
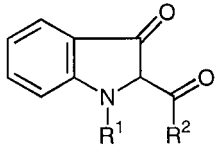


128

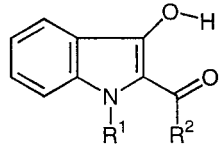


129

There seems to be only one report on a 1,2-dihydroxyindol-3-one (96TL43). 2-Acyloxindoles **130** (71JOC777; 82MI1; 86ZOR2434) can exist in several tautomeric forms. The hydroxy tautomer **131** seems to be the preferred one (74AP523; 79JHC661; 80AP405; 81AP852; 84JHC283; 86AP108; 94MI1, 94MI3, 94MI4). The same holds for 3-hydroxyindoles with a vinylogous carbonyl group in position 2 (91JHC1869, 91KGS343, 91KGS1199).



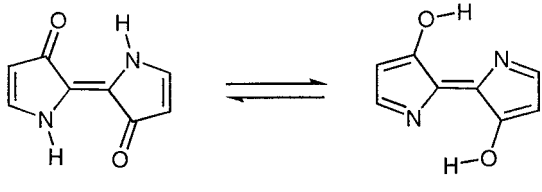
130



131

6. *Bis(pyrryl) Analogs of Indigo*

The intramolecular hydrogen transfer (both for single and double transfer) in the bis(pyrryl) analog of indigo (Scheme 17) was studied computationally by using the CNDO/2 method (with only partial optimization) (77ZC297). In line with expectations the double-proton transfer reaction has a higher energy barrier than the single-proton transfer. Whether there is a real transition state for the double-proton transfer is unknown.

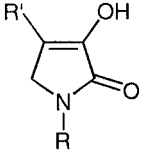


SCHEME 17

F. Potential Dihydroxypyrroles and -Indoles

1. *Oxygen Functions in 2,3-Positions*

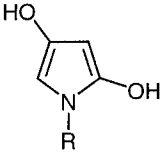
As already mentioned in the previous review (76AHCS1, p. 246), potential 2,3-dihydroxypyrroles exist in the monoenol form **132.** Recent work has confirmed these observations (76LA476; 94MI5).



132

2. *Oxygen Functions in 2,4-Positions and Aza-Analogs*

2,4-Dihydroxypyrroles **133** (tetramic acids) have been shown to exist as keto-enol **134** and diketo tautomers **135** [72JCS(P1)2121]. The equilibrium depends upon the solvent. Whereas in $CDCl_3$ exclusively the keto form **135** was observed, in [D_6]DMSO the keto-enol form **134** was also present (for R = H, Me) (76BCJ3287; 93S216). N-Protected 5-substituted tetramic acids have been shown to exist as the enol tautomers of type **134** in [D_6]DMSO [87JCS(P1)1177]. For further examples see 96JHC825 and 97JCS(P1)3543.



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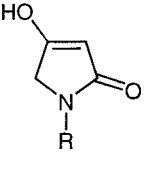

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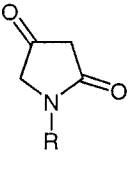
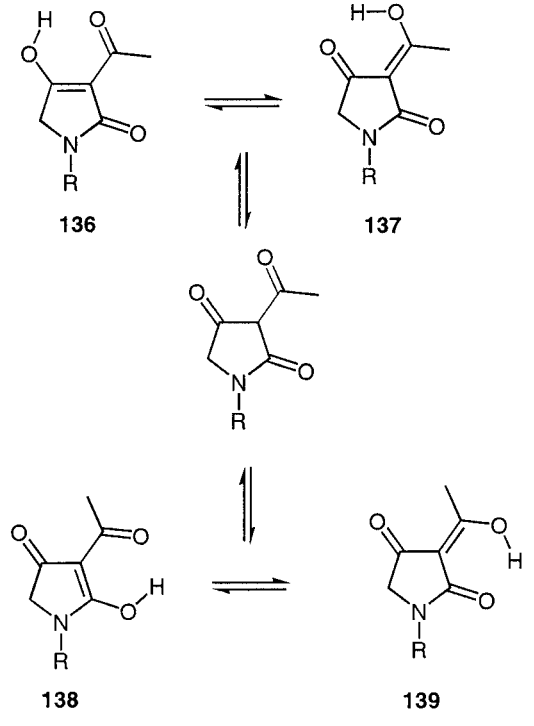


135

3-Acylpyrrolidin-2,4-diones (3-acyltetramic acids) constitute a growing class of natural products displaying a wide range of biological activities [e.g., erythroskyrin (90CC765), tirandamycin (71JA4943; 86JA5549), malonomycin (78T223), magnesidin (74TL983), streptolydigin (63JA4038), ikarugamycin (72TL1181; 87JA6403, 87TL31), tennazonic acid (59BJ332)]. This attracted considerable interest to this class of compounds [94JCS(P2)1271].

As has already been pointed out for 3-acyl-tetronic and -thiotetronic acids, the corresponding 3-acyl-tetramic acid can exist as "internal" tautomers (**136** ⇌ **137, 138** ⇌ **139**) as a result of prototropy between the two oxygen atoms and as "external" tautomers (**136, 137** ⇌ **138, 139**) as a result of rotation of the side-chain acyl group.

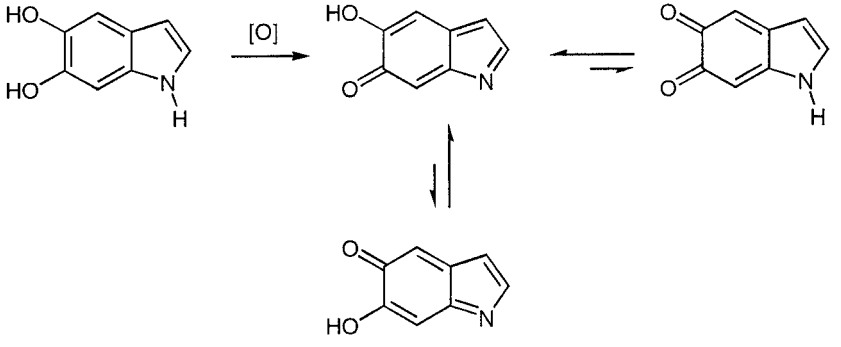


These equilibria depend to a considerable extent both on the substitution and on the solvents. Steyn and coworkers have reported extensive studies on the tautomerism of these compounds [78TL4707; 80JCS(P1)1057; see also 94JCS(P2)1271]. Two sets of peaks have been observed (^{1}H and ^{13}C NMR) for certain protons and carbon atoms in $CDCl_3$. Tautomers **136** ⇌ **137** (and also **138** ⇌ **139**) are rapidly interconverting and the NMR shows signals in which chemical shifts are weighted averages of those tautomer pairs. The interconversion between tautomers **136/137** and **138/139** ("external" pairs) is a slow process on the NMR time scale and separate NMR signals can be detected. From a detailed study it was concluded that **137** and **139** (*exo* enol forms) are the dominant tautomers in the equilibrium (with **139** dominating). An X-ray structure determination clearly established that

3-acetyl-5-isopropylpyrrolidine-2,4-dione exists in the crystal as a tautomer of type **139** [80JCS(P1)1057]. For further work on 5-substituted 3-acyltetramic acids see 99SL873. The solvent-dependent tautomerism of 1,5,5-trimethyl-3-acetyltetramic acid has been investigated by ^{1}H and ^{13}C NMR (90JPR319).

From NMR spectra in $CDCl_3$ it was concluded that in *N*-acetyl-3-butanoyltetramic acid the tautomeric pair **136/137** predominates [94JCS(P2)1271]. The study of the X-ray crystal structure of this compound revealed that in the solid state it exists as tautomer **136** [94JCS(P2)1271]. For further work in this field see 76BCJ1161, 76JHC533, 78BCJ651, and 79JCS(P2)1605. Semiempirical studies concerning these tautomeric equilibria have been reported [83TL4757; 90JCS(P1)1959, 90MI4].

A tautomeric equilibrium between quinone and quinone methide tautomers has been proposed to exist for the compounds which are obtained by oxidation of 5,6-dihydroxyindole (Scheme 18) (92TL3045).

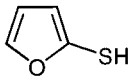


SCHEME 18

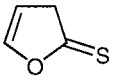
IV. Compounds with Potential Mercapto Groups

A. MERCAPTOFURANS AND -BENZOFURANS

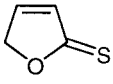
^{1}H NMR and IR spectra of 2-mercaptofurans show only the presence of the thiol isomers **140** with no indication of thiolactone tautomers **141, 142** [77ACS(B)198]. For further references see 69BCJ3068, 76T3023, 79JOC4140, 82DOK403, 89TL5013, 90PS111, 94KGS767, 94KGS891, and 95BCJ2319.



140



141



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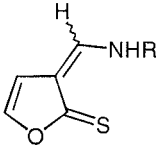

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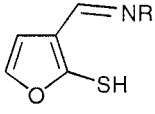

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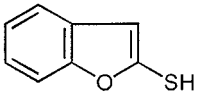

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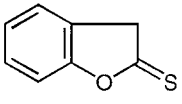


146

The thione form **143,** however, is favored in 2-mercaptofuran-3-aldimines over the corresponding thiol **144** (92MI2, 96RCR307). 2-Mercaptobenzo [*b*]furan **145** is in an equilibrium with the thione tautomer **146** in a ratio of 1 : 1 in $CDCl_3$ (95JOC6455) or in benzene (95JOC7941). For further references to 2-mercaptobenzofurans see 81ZOR1316, 82KGS1335, 82KGS1338, and 85KGS598.

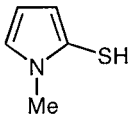
3-Mercaptofurans also exist exclusively as mercapto isomers [77ACS (B)198].

B. Mercaptothiophenes and -Selenophenes and Their Benzologs

2-Mercaptothiophene and -selenophene show only the presence of the mercapto isomer [77ACS(B)198; 86HC1; 96RCR307]. The only report (71BSF3547) of 2-mercaptoselenophene existing in the thione form has been disproved (97KGS500).

C. Mercaptopyrroles and -Indoles

1-Methyl-1*H*-2-pyrrolethiol exists in solution at equilibrium as a tautomeric mixture of **147, 148,** and **149** with 1-methyl-2,5-dihydro-1*H*-2-pyrrolothione **149** dominating (97T13079, 97T16783).



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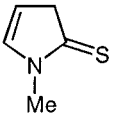

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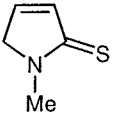

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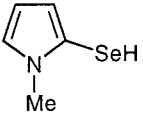

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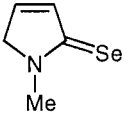


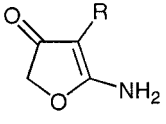
151

1-Arylpyrrole-2-thiols were formulated to be thiol tautomers (87JHC1157), but according to ^{13}C NMR spectra, N-unsubstituted analogs, 2,5-dihydro-1*H*-pyrrole-2-thiones, were reported to exist as thiono tautomers (C=S resonances) [92JCS(P1)899; 97JCS(P1)885]. 1-Methyl-1*H*-2-pyrroleselenol was observed as a mixture of **150** and **151** (in ratio 10/90 in CCl_4) (97T13079, 97T16783) (for further references see 75TL3089; 85MI1). 2-Mercaptoindoles [e.g., *N*-Boc-3-methylindole-2-thiol (92JA5566)] and 3-mercaptoindoles (e.g. *N*-benzylindole-3-thiol [97JCS(D)1857]) exist as thiol tautomers.

V. Compounds with Potential Amino Groups

A. Aminofurans

2-Aminofurans are known to be very unstable compounds, unless the ring bears several electron-withdrawing groups. They can be trapped as *N*-arylidene compounds [82AHC(30)168, 82AHC(31)237; 85LA51 and references cited therein]. 2-Amino-3-methyl(phenyl)furan-4(5*H*)ones **152** were formulated as keto tautomers [84JCS(P1)1539]. 5-Amino-4-hydroxy-2-phenylfuran-3-one was first formulated as imine **153,** but later the tautomeric enamine form **154** was preferred (91JOC3080, footnote 17). 2-Acyl-3-aminofurans of types **155** and **156** are available by a Thorpe cyclization reaction. These compounds have been formulated as furanones (84LA1702).



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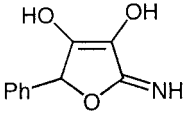

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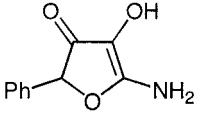

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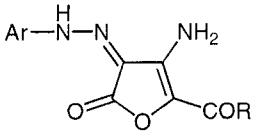
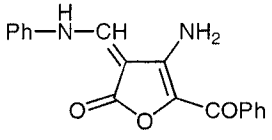


155

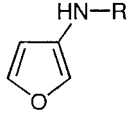
R=Me, Ph



156

2-Acyl-3-aminobenzo[*b*]furans also exist as amino tautomers (76JPR 313).

In contrast to 3-hydroxyfuran the corresponding 3-acylaminofurans **157** exist as such and not as 3(2*H*)-furanimines (according to ^{1}H and ^{13}C NMR). Interestingly, the addition of D_2O causes the gradual disappearance of the NH and the H-2 signals in ^{1}H NMR spectra (for R = $CO_2{}^{t}Bu$). The parent compound (3-aminofuran; **157,** R = H) could not be isolated (82T2783).



157

R = $CO_2{}^{t}Bu$, CO_2Me

B. Aminothiophenes

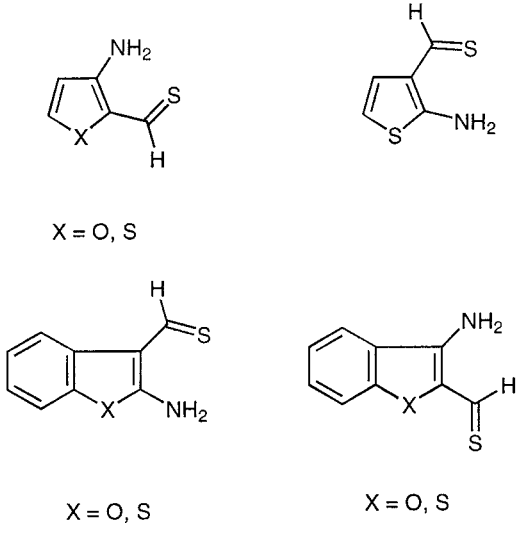
2-Aminothiophenes have been known for a long time (1885CB1490; 13LA17; 76AHCS1, p. 259; 86HC631). In 1960 it was proved that 2-aminothiophene exists exclusively in the amino form (60MI2). Recently it was shown that for **158a,b** there is a tautomeric equilibrium between the amino form **158** and the corresponding imino derivative **159** (in CCl_4 the ratio **158a/159a** is about 1 : 7; **159a** probably being an *E* isomer). More polar $CDCl_3$ shifts the equilibrium further to the imino form (in a mixture $CCl_4/CDCl_3$ = 1/1 the ratio **158a/159a** is 1 : 15).

158 **159**

a: X = O, R = Me
b: X = O, R = Ph
c: X = S, R = Me
d: X = S, R = Ph

In the case of **158b** the amino form predominates in $CDCl_3$ (**158b/159b** = 10/7). Compounds **158c** and **159d** showed only NMR signals attributable to the amino tautomer (98TL2433; 99Diss1, 99UP2). For a review on 2-aminothiophenes by the Gewald reaction see 99JHC333.

Since Woodward's work on the synthesis of chlorophyll *a* (60JA3800) it is known that the intrinsic unstable thioformyl moiety can be stabilized by the delocalization effect of heterocyclic systems. Recently the synthesis of 2-amino- and 3-aminothioformylthiophenes (and furans) and the corresponding benzo derivatives (Scheme 19) has been reported (96S1185). These compounds exist as amino tautomers (91S609; 96S1185).

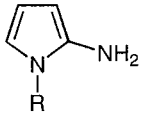


SCHEME 19

C. AMINOPYRROLES AND -INDOLES

Since the last review on tautomerism (76AHCS1, p. 260; see also 92HC299) some progress has been made in the synthesis of these compounds. 2-Aminopyrroles can exist either as amino or imino tautomers. Early theoretical calculations predict the amino tautomer **160a** to be more stable than the imino forms **161a** and **162a** (70JA2929), seemingly at variance with an observation reported in 1968 that 1-acetyl-2-amino-4,5-dimethylpyrrole exists in the imino form (68TL4605). Subsequent ^1H and ^{13}C NMR investigations revealed that this compound is in fact the amino tautomer (95JHC985). Recently the first route to 2-aminopyrrole **160a** and 1-substituted derivatives **160b-e** without further substitution in the ring was reported [95TL9261; 99JCS(P1)1433]. ^1H and ^{13}C NMR data revealed that these compounds exist as amino tautomers. Theoretical calculations for

160a [gas phase; HF/6-311++G(d,p)//MP2/6-31G(d,p) with correlation effects on the QCISD(T)/6-31+G(d,p) level; calculations in solution with Monte-Carlo – Free Energy Perturbation] indicate that the amino tautomer is the most stable form in chloroform and in water.



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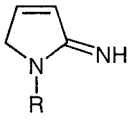

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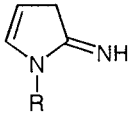
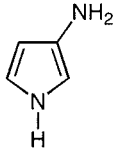
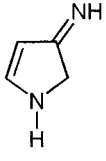


162

a: R=H, b: R=Me, c: R=Et, d: R=*t*-Bu, e: R=Ph



163

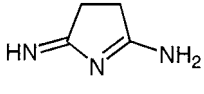


164

According to these theoretical models for 2-amino-1-methylpyrrole **160b,** both the amino and imino tautomers should be observable in water [99JCS(P2)1433]. According to DFT calculations (B3LYP/6-31G*; gas phase) **160a** is more stable than **161a** and **162a** by 1.8 and 2.8 kcal/mol, respectively (99UP1).

An electron-withdrawing group confers stability to 2-aminopyrroles. Several 2-amino-4-cyanopyrroles have been reported [50HCA273, 50HCA658; 75JCS(P1)1910]. For further work on 2-aminopyrrolines see 87MI5.

2-Amino-3-cyanopyrroles exist in solution as amino tautomers. They undergo protonation at the exocyclic nitrogen in DMSO/TFA and protonation C-5 in TFA (68TL4605; 87T5225; 95JHC985). Although it was suggested earlier (76AHCS1, p. 260) that succinimidine exists in the diimino-form, recent work has shown that this compound is best represented by **165** (84BSB191).

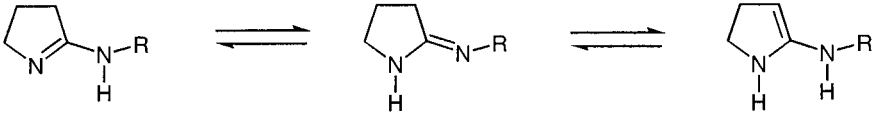


165

The energy difference between 3-aminopyrrole **163** and the corresponding imino tautomer **164** was calculated by this method as 9.2 kcal/mol in favor of the amino tautomer (99UP1). Interestingly, 1-(triphenylmethyl)-3-

aminopyrrole has been reported to exist in chloroform solution entirely as imino tautomer [83JCS(P1)93].

By means of ^1H and ^{13}C NMR spectroscopy it was found that 2-(methylamino)-1-pyrroline (R = Me) is present in solution mainly in the amino form. For the corresponding *N*-phenyl derivative an equilibrium between 2-aminopyrroline, imino, and 2-amino-4,5-dihydropyrrole tautomers is found (Scheme 20) (87MI5).



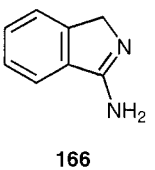
R = Me, Ph

SCHEME 20

Since the last review (76AHCS1, p. 261) 2-aminoindoles have been reported on repeatedly, especially compounds with electron-withdrawing substituents at C-3. Generally, these aminoindoles were formulated as amino tautomers [86TL4281; 89S530; 91KGS400, 91MI3, 91S609; 92JCS(P1) 275; 93LA465; 95JOC2254; 96S1185, 96TL4931; 97TL6909]. 3-Aminoindoles have also been formulated generally as amino derivatives [80JCR(M)833; 83JHC495; 90AP715; 91JHC379, 91JHC557; 93T1431; 95G151].

D. AMINOISOINDOLENINES

The amidine tautomerism of 1-aminoisoindolenine (**166** ⇌ **167**) has been studied by the MNDO method. According to these data tautomers **166** and **167** have nearly identical enthalpies [ΔH_f^0 (**166**) = 41.9 kcal/mol, ΔH_f^0(**167**) = 41.8 kcal/mol] (93MI2). Recalculation revealed the following values: ΔH_f^0 (**166**) = 45.2, 38.2, 58.9, 46.5 kcal/mol; ΔH_f^0 (**167**) = 41.5, 32.7, 56.7, 45.0 kcal/mol (MNDO, MINDO/3, AM1, PM3) (99UP1).



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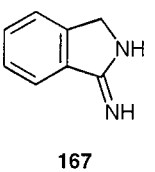

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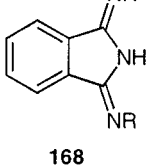
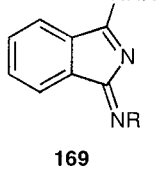


168



169

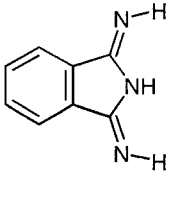
a: R=H
b: R=Me
c: R=CH_2Ph
d: R =aryl

Phthalic imidine was shown by ^{13}C NMR to be present in [D_6]DMSO solution as a 1 : 5 mixture of **168a** and **169a** (84BSB459). This result is at variance with earlier UV measurements, which seemingly indicated that phthalic imidine exists entirely in its 1,3-diimino form **168a** (56JCS4135). The amino tautomer **169a** also predominates in $CDCl_3$, D_2O, and CD_3OD. The parent compound **168a** has been studied computationally by the AM1 method (97MI9, 97KGS1074). There are at least three different geometric isomers **170–172** where **170** is the most stable one.

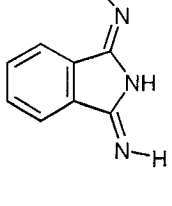
The N^1,N^3-dimethyl derivative **168b/169b** also exists as a tautomeric mixture in which **169b** predominates (84BSB459). According to ^1H NMR spectra the N^1,N^3-dibenzyl derivative exists as 1*H*-isoindole **168c** (83MI5; 84BSB 459; 88MI5).

The ^1H NMR spectra of the corresponding *N*-aryl derivatives (**168d, 169d**) are fairly complex (several *E/Z* isomers), but it was concluded that tautomers **168** and **169** are both present. The equilibrium strongly depends on the polarity of the solvent, the concentration, the temperature, and the nature of the substituent R.

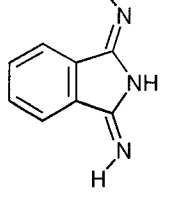
In nonpolar solvents, regardless of the substituents, all of these compounds seem to exist mainly in the tautomeric form **168.** In polar solvents, the position of the equilibrium is strongly affected by the nature of the substituent R (83MI5; 88MI5).



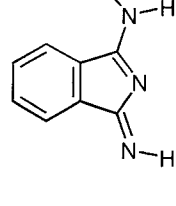
170



171



172



173

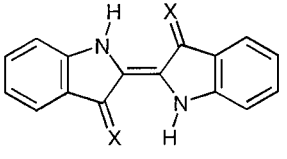
The amino tautomer **173** was found to be the least stable one [$\Delta\Delta H_f^0$ (**170–173**) = 3.9 kcal/mol (AM1)]. A recalculation gave a slightly different stability range [ΔH_f^0 (**170**) = 81.1 kcal/mol, [ΔH_f^0 (**171**) = 83.2 kcal/mol, [ΔH_f^0 (**172**) = 85.9 kcal/mol, ΔH_f^0 (**713**) = 85.1 kcal/mol] (99UP1). The transition states for the isomerization reaction **170** → **172** and **170** → **173** have also been reported (97KGS1074).

Tautomeric interconversions of 1,3-diimino-isoindolenine and its nitro and amino derivatives have been studied theoretically by the AM1 method (97MI9).

The tautomerism of 3-iminoisoindolenin-1-ones have also been investigated. Both possible tautomers have been detected (83BSB965).

E. Indigo and Diiminoindigo

The tautomerism of indigo **174** (X = O) has been studied in detail (86JPC2901) (for reviews see 66CB2136; 88MI4; 95MI3; 97MI6). In its electronic ground state only the trans configuration has been observed. Semiempirical calculations have confirmed that tautomers **175** (X = O) (77MI4; 78MI1) and **176** (X = O) have energies substantially higher (ΔH_f^0 (**174**) = 39.0, 10.8 kcal/mol; ΔH_f^0 (**175**) = 54.1, 20.9 kcal/mol, ΔH_f^0 (**176**) = 97.8, 64.2 kcal/mol; AM1, PM3 for X = O) (99UP1).



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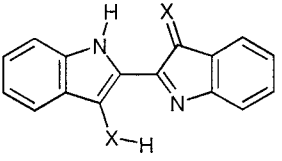

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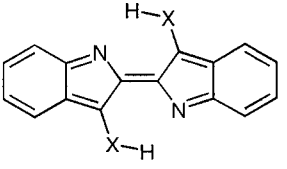
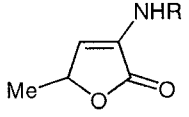


176

Phototautomerization of **174** (X = O) to **176** (X = O) has been postulated as a radiationless pathway which effectively quenches fluorescence of **174** (X = O). By contrast, quantum mechanical calculations (CNDO, CNDO/S) indicate a preferential formation of **175** (X = O) over **176** (X = O) (77MI4; 78MI1). A combination of fluorescence and IR studies indicate the absence of proton transfers in the excited state of **174** (X = O) (96JA12459; see also 77MI4). Diiminoindigo (**174,** X = NH) has been shown to adopt the tautomeric form **175** (X = NH). It was reported that semiempirical calculations (AM1) are in agreement with this observation [ΔH_f^0(**174,** X = NH) = 140.5 kcal/mol, ΔH_f^0(**175,** X = NH) = 138.4 kcal/mol], although this difference may not be large enough to support the experimental results (96JA 12459). Recalculations revealed that these val-ues have probably to be exchanged [ΔH_f^0 (**174,** X = NH) = 138.9 kcal/mol, ΔH_f^0 (**175,** X = NH) = 140.2 kcal/mol] (99UP1). By variable temperature ^{1}H NMR measurements, it was possible to confirm that **175** (X = NH) tautomerizes to the corresponding degenerate form via a double-proton transfer [$\Delta H^{\#}$ = 5.4 ± 0.3 kcal/mol; $\Delta S^{\#}$ = −16 ± 2 cal/(mol • K), in a mixture $CDCl_3/CDCl_2F/CDClF_2$ = 1:5:5] (96JA12459). For further work see 75AG63.

VI. Compounds with a Potential Hydroxy and a Potential Amino Group

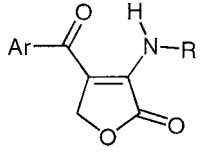
The potential 2-hydroxy-3-aminofurans exist as enaminoketones **177** (89T6631).



177

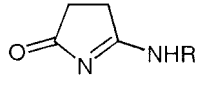
R = H, Ac

The potential 4-aroyl-2-hydroxy-3-aminofurans exist as γ-lactones **178** (R = 6-aminouracil) (91JHC1501).



178

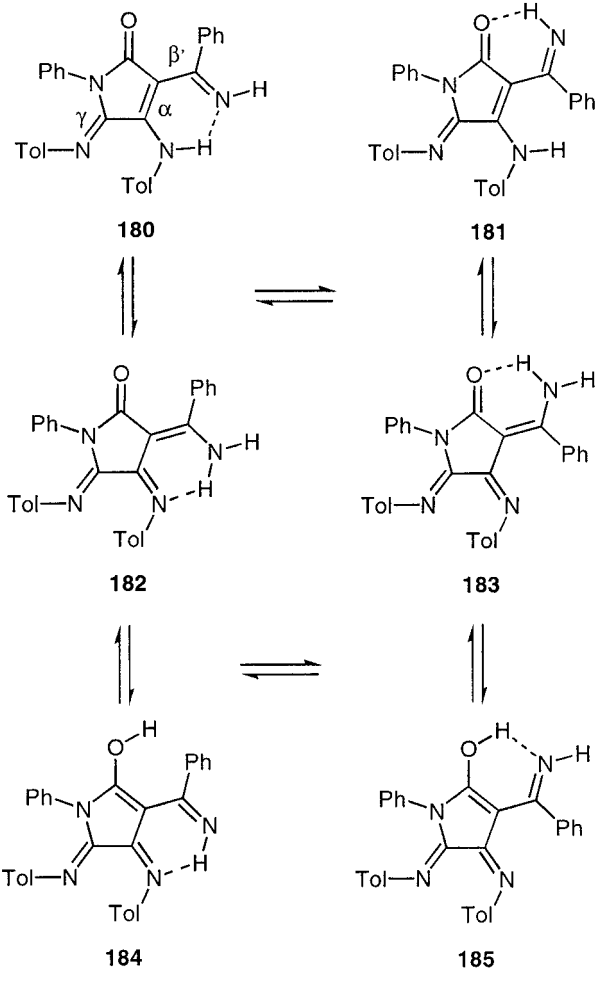
2-Aminopyrrolin-5-ones are present in solution as amino tautomers **179.**



179

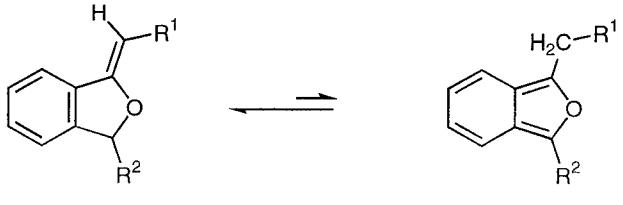
The tautomerism of aza-analogs of 3-acyltetramic acids of type **180** have been investigated by Langer and coworkers (97LA2553).

There are two sets of interchanging tautomers (**180/182; 183/185**) arising through proton transfer together with three pairs (**180/181; 182/183; 184/185**) arising from the rotation of the side chain. Structural mobility was detected by variable-temperature ^{1}H NMR. Detailed spectroscopic investigations (^{1}H, ^{13}C, IR, UV) revealed that the pair **180/182** (in a rapid equilibrium) dominates in solution. AM1 calculations have shown that tautomers of type **184** and **185** are least stable (stability range: **182** > **183** > **181** ≅ **180** > **184** > **185;** ΔH_f^0 (rel. values in kcal/mol): −13.58, −5.42, −0.04, 0.00, 8.78, 14.35). (97LA2553). A recalculation revealed the following values: −11.27 (**182**), −13.52 (**183**), −1.73 (**181**), 0.00 (**180**), 10.83 (**184**), 10.40 (**185**) (99UP1).



VII. Compounds with Potential Methyl Groups

Treatment of benzylidenephthalans of type **186** with dienophiles in the presence of catalytic amounts of an acid results in the formation of Diels–Alder adducts of the corresponding benzo[*c*]furans **187** [74T2603; 80JOC1817; 81JOC4083, 81JOC4658; 86JOC3973; 88JOC1841; 89S942; 91JOC1882; 99AHC(73)1].



186 **187**

188 **189**

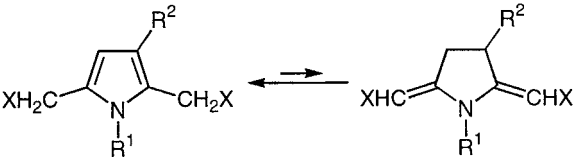
Although an equilibrium **186** ⇌ **187** can be anticipated, compound **187** could not be detected by ^{1}H NMR or UV spectroscopy (74JOC3648). Bornstein and coworkers succeeded in the preparation of **187** (R^1 = Ph, R^2 = H) (76TL2507; 77JA8248) and observed a rearrangement to **186** (R^1 = Ph, R^2 = H) at room temperature. A dramatic increase in the rate of the rearrangement was observed in the presence of acids. Semiempirical (AM1, PM3) and density functional theoretical studies (B3LYP/6-31G*) have been reported for tautomeric equilibria of this type (**188** ⇌ **189** and benzannulated compounds) (99MI2). According to these calculations the equilibrium depends on the substitution. *Linear* benzannulation shifts the equilibrium to the alkylidene compounds, whereas an *angular* benzannulation may lead to tautomeric equilibrium where the benzo[*c*]furan isomer predominates. These theoretical predictions have not yet been confirmed by experimental studies.

Flitsch and coworkers investigated the acid (TFA)-catalyzed tautomeric equilibria of 2,5-dialkylpyrroles of type **190** (78CB2401). The equilibrium depends on the substitution in these compounds.

VIII. Other Substituted Furans, Thiophenes, Pyrroles, and Their Benzo Derivatives

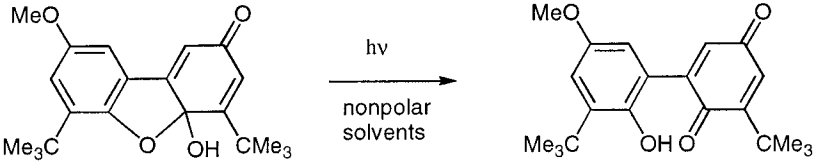
A. Ring-Chain Tautomerism

The phototautomerization of a dibenzo-2-(4a*H*)-one **192** has been reported (83AJC1603).



190 **191**

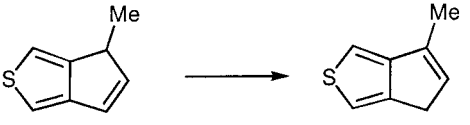
	X	R^1	R^2	Ratio **190/191**
a:	CN	Me	H	8/1
b:	CN	Ph	H	30/1
c:	CO_2Et	Me	H	only **190**
d:	CO_2Et	Ph	H	only **190**
e:	CN	Me	Me	only **190**
f:	CN	Me	CN	only **190**



192

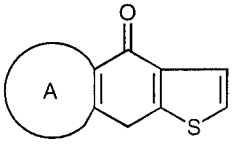
B. Substituent Tautomerism

The base-catalyzed tautomerization of 4-methyl-4*H*-cyclopenta[*c*]thiophenes **193** to the corresponding 6-methyl derivative **194** has been investigated quantitatively. Second-order rate constants and activation parameters have been determined (75CS42).



193 **194**

Annulated thiophenes of types **195** and **197** (A: benzo, naphtho) were studied concerning keto-enol tautomerism. The ring fusion has a remarkable influence upon these equilibria. Whereas for the *c*-fused thiophenes **197** only keto tautomers were present, for *b*-fused derivatives **195** also the enol forms **196** were found (the equilibria are solvent dependent) (82JOC705).



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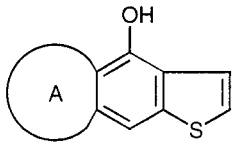

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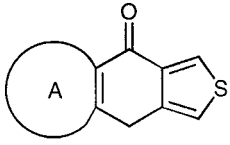

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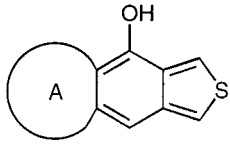


198

Similar results have been reported for 4,8-dihydrobenzo[1,2-*c:* 4,5-*c′*]dithiophene-4-one (74JOC2239). In line with expectations, only the keto form of this compound was detected.

A tautomeric equilibrium of 4-hydroxy-benzo[*c*]furan-3(1*H*)-ones of type **199** has been reported [R, R = Me, $(CH_2)_4$, $(CH_2)_5$] (89KGS24).

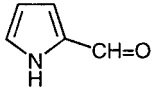
199

C. Oligopyrroles and Porphyrins

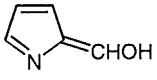
Since 1975 the tautomerism of oligopyrroles, porphyrins, and related compounds has been studied intensively. A large amount of data has been obtained. As this subject has been reviewed comprehensively [83MI3; 89MI4; 97LA565, B-97MI1, 97MI08; for further references see 77JA1601; 82JA2376; 83AG639; 84JA4059; 85JA2979, 85JCS(P2)395; 86JA3608, 86JA3856, 86JA6449; 87AG914, 87JA2335; 88JA336, 88JA8336, 88JOC1132; 89AG84, 89CC90; 90JCS(P1)1945; 92JOC1833; 93JA4554; 94JA6593; 97CR2267, 97IC6103, 97LA1345, 97MI8; 98AG(E)177, 98AG187, 98JOC4829; 99JOC433], these results are not discussed in this chapter.

D. Others

According to computational studies, pyrrole-2-carbaldehyde **200** is more stable than the corresponding tautomer **201** by 7.05 kcal/mol (CNDO/2) and 18.9 kcal/mol (STO-3G) (90MI5).



200



201

DFT calculations (B3LYP/6-31G*) support these earlier results [E(**200**) = −323.49543, E (**201**) = −323.47262; in hartrees] (99UP1).

A mass spectrometric investigation of 3-nitrosopyrrole was reported (77MI3).

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The Tautomerism of Heterocycles: Five-Membered Rings with Two or More Heteroatoms

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The material discussed in this chapter concentrates on data that has been published since the mid-1970s. It is supplemental to that of the corresponding chapter of the monograph [76AHC(S1), p. 266], which surveyed the literature on tautomerism of azoles up to 1975. We attempted to follow the classification of that previous review, of which the principal features are (1) the distinction between tautomeric rearrangements involving only ring-nitrogen centers (annular tautomerism) and those accompanied with transformations in ring-side groups and (2) the arrangement of the material according to the compounds' main structural types.

From the structural point of view, four principal types of tautomeric processes relevant to the heterocyclic compounds under consideration exist. These include (1) tautomerism involving annular centers, (2) side-chain tautomerism associated with transformations involving functional group(s) attached to the rings, (3) ring-chain tautomerism as a special case of the side-chain tautomerism accompanied by ring closing, and (4) valence tautomerism. For types 1 and 2, tautomeric interconversions may occur through migration of a proton (prototropic tautomerism) or a heavier element-centered group (elemento- or metallotropic tautomerism), both intramolecularly and intermolecularly. Ring-chain tautomerism is almost exclusively a nonprototropic process.

Additional sections of this chapter cover (1) tautomeric reactions of azoles and their derivatives in electronically excited states and (2) stabilization of certain tautomers in their metal complexes.

I. Annular Tautomerism

A. Scope and Definition

Annular tautomerism has been defined as the class of tautomeric rearrangements in which only annular nitrogen or carbon atoms are involved [76AHC(S1), p. 266]. In azoles, the latter case is frequently energetically un-

favorable due to the lack of aromaticity in the nonconjugated isomers; thus it is displacements of a proton or other migrating group between two or more ring-nitrogen centers which constitute the phenomenon of annular tautomerism. These displacements may occur in both intramolecular and intermolecular modes. To be described as tautomeric rearrangements they must fall into the range of thermodynamic and kinetic scales characteristic of these processes. One of the authors of this chapter proposed in 1981 (81ACR210; 88MI1, p. 12) the values given in Eqs. (1) and (2). Equation (1) relates to the sensitivity at that time of the available techniques for the observation of the minor tautomer; it could be argued that with the improved current methodology the value should be considerably higher. Equation (2) serves to differentiate tautomeric rearrangements from slower processes in which lifetimes are sufficiently long to permit the preparative separation of the individual compounds: again, the absolute value is difficult to define and it obviously depends on the temperature of the observation.

$$\Delta G^\circ \leq 20 \text{ kJ mol}^{-1} \tag{1}$$

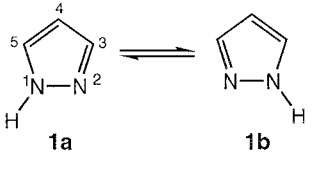
where ΔG° is difference between the free energies of tautomers and

$$\Delta G^* \leq 100 \text{ kJ mol}^{-1}, \tag{2}$$

where ΔG^* is activation energy for the tautomeric reaction.

The first condition is obviously met for the degenerate tautomeric reactions which were also termed as autotropic rearrangements [76AHC(S1), p. 268]. An illustrative and the most thoroughly studied example of such a tautomeric rearrangement is the interconversion of the degenerate isomers of pyrazole **1** (Scheme 1).

Despite the seeming simplicity of this it has a rather complicated mechanism which can change drastically depending on the medium and the substitution in the ring. Understanding the peculiarities of these mechanisms and gaining deeper insight into the structural correlations governing the positions of tautomeric equilibria as well as accumulation of exact quantitative data on the kinetics of proton and other group migrations are all important contributions to the vast domain of annular tautomerism of azoles made since the mid-1970s. Progress in this area is a direct result of the significant developments in physical methods, primarily multinuclear NMR spec-



1a **1b**

SCHEME 1

troscopy, X-ray crystallography, and quantum mechanical techniques, which have been applied extensively to the study of annular tautomerism. The progress for pyrazole and its derivatives is particularly pronounced and these represent the group of heterocyclic compounds whose tautomeric transformations have been studied thus far in most detail.

B. Prototropic Annular Tautomerism

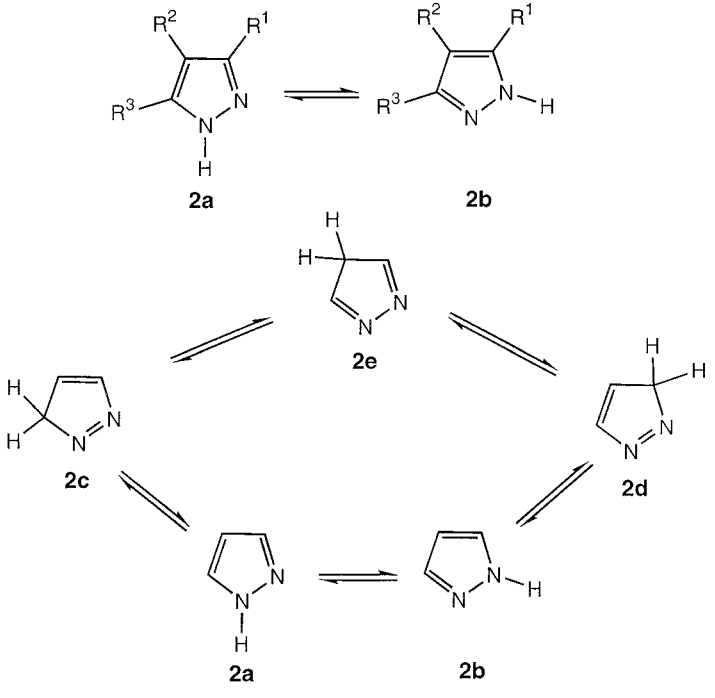
1. *Pyrazole and Its Derivatives*

It has been recognized [76AHC(S1), p. 272; 84CHEC-I(5)167; 87AHC (41)187; 96CHEC-II(3)1] that virtually all N-unsubstituted pyrazoles in solution are mixtures of annular tautomers whose relative populations depend on the nature of the substituents R^1 and R^3, the temperature, and the nature of the solvent.

Apart from the 1*H* and 2*H* tautomers **2a** and **2b,** isomeric forms in which the migrating proton takes up its position on one of the carbon atoms in the ring are formally possible. For the case of unsubstituted pyrazole **2,** $R^1 = R^2 = R^3 = H$, the tautomeric equilibrium should be represented by the scheme involving 4*H* **2e** and a pair of degenerate 5*H* species **2c** and **2d** (Scheme 2).

However, isomers **2c**–**2e** are energetically highly unfavorable in comparison with **2a,b.** The STO-3G estimates of the relative energies, ΔE, of **2c,d** and **2e** are respectively 81.2 and 87.4 kJ mol^{-1} higher than **2a,b.** The energy barrier to **2a,b** $\rightleftharpoons$ **2c,d** exceeds 210 kJ mol^{-1} [86BSF429]. A reverse order of stabilities of **2c,d** (ΔE = 121.7 kJ mol^{-1}) and **2e** (ΔE = 101.7 kJ mol^{-1}) has been obtained in subsequently more accurate MP2/6−31+G* calculations (95JOC4721). These values, however, are even larger than those obtained with the use of the STO-3G model. They are out of the limits of the tautomeric energy scale as described by Eqs. (1) and (2) and hardly subject to qualitative correction at higher levels of approximation. The possible analogy between the isomerization process **2a** $\rightleftharpoons$ **2b** and the [1,5] hydrogen shift in cyclopentadiene has been discussed [98JCS(P2)2497]. If pyrazole prototropy is considered strictly as an intramolecular proton transfer, the energy barrier for this tautomerization is too high for the process to be allowed. This indicates the necessity of taking into account such factors as solvent effects and association and removes azole prototropy from the Woodward–Hoffmann domain.

a. *Position of the Tautomeric Equilibrium **2a** $\rightleftharpoons$ **2b**.* The data on the thermodynamic parameters of this type of equilibria are collected in Table I.



SCHEME 2

Whereas early approaches to evaluation of positions of these equilibria were based mainly on the measurements of basicities of the tautomeric compounds **2** and their NMe derivatives used as the structural models of particular tautomers **2a** and **2b** [76AHC(S1), p. 22], in the past decades manifold NMR spectral techniques have acquired greatest significance for quantitative description of the equilibria, dynamics, and mechanisms of interconversions of the tautomers. The simplest and most versatile method of detection of the tautomeric equilibrium and determination of the equilibrium constant, K_T, is the use of low-temperature ^{1}H NMR. In those cases when lowering the temperature of a solution allows one to slow down the rate of the proton exchange between the two tautomers, both of them can be separately observed in the NMR spectrum and their relative populations are assessed from the intensities of directly observed spectral signals. An example of the successful application of the ^{1}H NMR spectral method for the determination of K_T is given in the case of 3(5)-phenyl-5(3)-methylpyrazole **2a,** R^1 = Ph, R^2 = H, R^3 = Me, in a series of solvents [92JCS(P2)1737].

As seen from Table I, no systematic data obtained under identical conditions are available regarding the influence of substituents in the ring on the

TABLE I

TAUTOMERIC EQUILIBRIA AND PREFERRED TAUTOMERIC FORMS OF PYRAZOLES 2

Compound[a]	Tautomerism results	References
R^1 = F (R^2 = R^3 = H)	MP2/6-311G**: $\Delta E = -14.4$ kJ mol^{-1}	99H(51)355
R^1= Me (R^2 = R^3 = H)	H_2O (20°C): $\Delta G^0 = -0.4$ kJ mol^{-1}. $K_T = 1.17$	76AHC(S1), p. 273
	HMPT (256 K): $\Delta G^0 = 0.34$ kJ mol^{-1}. $K_T = 0.85$	81G477, 92JCS(P2)1737
	Solid: Both tautomers are present in equimolar amounts in the crystal of an inclusion compound of **2**[c, d]	88CL1061
	Gas phase (mass spectroscopy): $K_T \sim 1$	76AHC(S1), p. 274
	6-31G//6-31G: $\Delta E = -1.5$ kJ mol^{-1}	92JOC3938
R^1= $CH(C_6H_5)_2$ (R^2 = R^3 = H)	$CDCl_3$, DMSO-d_6 (room temp.): Both tautomers are present in nearly equal proportions.	93CJC678
R^1 = Ph (R^2 = R^3 =H)	HMPT (20°C): $\Delta G^0 = -3.4$ kJ mol^{-1}. $K_T = 4$	81G477
	HMPT-acetone (253 K): $\Delta G^0 = -1.98$ kJ mol^{-1}. $K_T = 2.57$	92JCS(P2)1737
	Gas phase (mass spectroscopy): $K_T \sim 1$	76AHC(S1)
	Solid: Exists in the **2b** form.	93CJC678
	6-31 G**//3-21G: $\Delta E = -0.7$ kJ mol^{-1}	95BCB383
R^1 = adamantyl	Solid: Both tautomers are present in 1 : 1 ratio	97JCS(P2)1867
R^1 = NH_2 (R^2 = R^3 = H)	6-31G//6-31G: $\Delta E = -5.1$ kJ mol^{-1}	92JOC3938
	MP2: $\Delta E = -5.4$ kJ mol^{-1}	98H(49)157
	B3LYP/6-31G**: $\Delta E = -11.3$ kJ mol^{-1}	98H(49)157
R^1 = NH_3^+ (R^2 = R^3 = H)	6-31G//6-31G: $\Delta E = 76.6$ kJ mol^{-1}	95JCS(P2)379
	AM1: $\Delta E = 42.7$ kJ mol^{-1}	95JCS(P2)379
R^1 = NMe_3^+ (R^2 = R^3 = H)	AM1: $\Delta E = 38.9$ kJ mol^{-1}	95JCS(P2)379
R^1 = N_2^+ (R^2 = R^3 = H)	DMSO-d_6 (room temp.): **2a** predominates[e]	95JCS(P2)379
	Solid: Only **2a**[c]	95JCS(P2)379
	6-31G**//6-31G: −62.7 kJ mol^{-1}	95JCS(P2)379
	AM1: −36.4 kJ mol^{-1}	95JCS(P2)379

(*continues*)

TABLE I—*Continued*

Compound[a]	Tautomerism results	References
$R^1 = N_3$ ($R^2 = R^3 = H$)	**2a** predominates	74JHC921
	AM1: −8.8 kJ mol^{-1}	95JCS(P2)379
$R^1 = CO_2Et$ ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): **2a** predominates	84OMR603
$R^1 = NO_2$ ($R^2 = R^3 = H$)	H_2O (25°C): **2a** predominates	75TAL819
	Solid: Only **2a**	97JPO637
	6-31G//6-31G: −1.2 kJ mol^{-1}; MP2/6-31G** + ZPE: 0.4 kJ mol^{-1}	97JPO637
$R^1 = C_6H_2(CH_3)_3$-2,4,6 ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): both tautomers in nearly equal proportions	93CJC678
	Solid: Only **2a**	93CJC678
$R^1 = C_6H_4OCH_3$-2 ($R^2 = R^3 = H$)	$CDCl_3$ (room temp.): **2b** predominates	92JA5039
	Solid: Only **2b**	93CJC678
$R^1 = C_6H_3(OCH_3)_2$-2,4 ($R^2 = R^3 = H$)	$CDCl_3$ (room temp.): DMSO-d_6 (80°C): only **2b**	93CJC678
	Solid: Only **2b**	93CJC678
$R^1 = C_6H_2(OCH_3)_3$-3,4,5 ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
$R^1 = C_6H_4NO_2$-4 ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
$R^1 = C_6H_4Cl$-4 ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
R^1 = 1-naphthyl ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
R^1 = 2-naphthyl ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	
R^1 = 9-anthryl ($R^2 = R^3 = H$)	$CDCl_3$ (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	
R^1 = 2-thienyl ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
R^1 = 2-pyridyl ($R^2 = R^3 = H$)	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678

R^1 = ferrocenyl (R^2 = R^3 = H)	$CDCl_3$, DMSO-d_6, THF-d_8: both tautomers are present in nearly equal proportion	93CJC678
	Solid: A mixture of both tautomers	93CJC678
R^1 = EtOCO (R^2 = R^3 = H)	DMSO-d_6: **2a** predominates, $K_T = 2.3$	99H(50)227
	Solid: only **2a**	99H(50)227
R^1 = R^2 = F, R^3 = H	MP2/6-311G**: $\Delta E = -16.5$ kJ mol^{-1}	99H(51)355
R^1 = Me, R^2 = Br, R^3 = H	DMSO-d_6 (room temp.): **2b** predominates	88CJC1141
	Solid: Only **2b**	88CJC1141
R^1 = R^2 = Me, R^3 = H	Solid: only **2b**	99AX(B)441
	B3LYP/6-31G**: $\Delta E = -1.8$ kJ mol^{-1}	99AX(B)441
R^1 = *i*-C_3H_7, R^2 = Br, R^3 = H	DMSO-d_6 (room temp.): **2b** predominates	93CJC678
	Solid: Only **2b**	93CJC678
R^1 = *t*-C_4H_9, R^2 = Br, R^3 = H	$CDCl_3$: **2b** predominates	93CJC678
	Solid: Only **2b**	93CJC678
R^1 = Ph, R^2 = Br, R^3 = H	Solid: **2a** is the major tautomer	92JCS(P2)1737
R^1 = Me, R^2 = NO_2, R^3 = H	Solid: Both tautomers can be isolated as individual crystal forms	94JCS(CC)1143
	Mixture **2a:2b** = 25 : 75 in the 1 : 1 : 1 complex with toluene and the host[g] compound HF/6-31G**: $\Delta E = 3.3$ kJ mol^{-1}	96JPO611 94JCS(CC)1143
R^1 = EtOCO, R^2 = Br, R^3 = H	DMSO-d_6: **2a** predominates, $K_T = 1.2$	99H(50)227
	Solid: only **2a**	99H(50)227
R^1 = EtOCO, R^2 = Me, R^3 = H	DMSO-d_6: **2a** predominates, $K_T = 2.3$	99H(50)227
	Solid: only **2a**	99H(50)227
R^1 = EtOCO, R^2 = Ph, R^3 = H	DMSO-d_6: **2b** predominates, $K_T = 0.67$	99H(50)227
	Solid: only **2a**	99H(50)227
R^1 = Me, R^2 = H, R^3 = Ph	HMPT (253 K): $\Delta G = -2.3$ kJ mol^{-1}. $K_T = 3.0$	92JCS(P2)1737
	Solid: Both tautomers are present	75JCS(P2)1068
	6-31G**//3-21G: 0.9 kJ mol^{-1}	95BSB383

(*continues*)

TABLE I—*Continued*

Compound[a]	Tautomerism results	References
R^1 = OEt, R^2 = H, R^3 = Me	H_2O: K_T = 30[f]	76AHC(S1), p. 273
R^1 = Br, R^2 = H, R^3 = Me	H_2O: K_T =23-31[f]	76AHC(S1), p. 273
R^1 = Me, R^2 = H, R^3 = CF_3	$CDCl_3$ (room temp.): **2b** overwhelmingly predominates	83IC774
	Solid: Only **2b**	93CJC678
R^1 = Me, R^2 = H, R^3 = *t*-Bu	$CDCl_3$, DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
R^1 = CF_3, R^2 = H, R^3 = *t*-Bu	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
R^1 = 2-thienyl, R^2 = H, R^3 = *t*-Bu	$CDCl_3$ (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
R^1 = CF_3, R^2 = H, R^3 = 2-thienyl	DMSO-d_6 (room temp.): **2a** predominates	93CJC678
	Solid: Only **2a**	93CJC678
R^1 = EtOCO, R^2 = H, R^3 = Me	DMSO-d_6: **2a** predominates, K_T = 4.0	99H(50)227
	Solid: only **2a**	99H(50)227
R^1 = EtOCO, R^2 = H, R^3 = Ph	DMSO-d_6: **2b** predominates, K_T = 0.82	99H(50)227
	Solid: only **2a**	99H(50)227
R^1 = H, R^2 = R^3 = $(CH_2)_4$	$CDCl_3$ (room temp.): both tautomers are present in nearly 1 : 1 proportions	93CJC678, 94NJC269, 97MI121
	Solid: both tautomers are present	
	6-31G*: −2.8 kJ mol^{-1}; AM1: 0.1 kJ mol^{-1}	93CJC678
		97MI189[g]

R^1 = H, R^2 = R^3 = Campho[2,3-*c*]	AcOH (room temp.): **2b** predominates	96MI18
	Solid: Only **2b**	93AX(C)724
	AM1: 17.2 kJ mol^{-1}	97MI189[g]
	PM3: 0.4 kJ mol^{-1}	96MI18
R^1 = H, R^2, R^3 = 4-($CH_2C_6H_4$-*o*)-5	DMSO-d_6 (room temp.): **2b** predominates	93CJC678
	Solid: Only **2b**	93CJC678
R^1 = H, R^2,R^3 = 4-[$(CH_2)2C_6H_4$-*o*]-5	$CDCl_3$ (room temp.): both tautomers are present in nearly equal proportions	93CJC678
R^1 = Me, R^2 = R^3 = $(CH_2)_3$	$CDCl_3$ (room temp.): **2b** predominates	93CJC678, 94NJC269
	Solid: Only **2b**	93CJC678
	6-31G*: 3.2 kJ mol^{-1}; AM1: 11.7 kJ mol^{-1}	97MI189[g]
R^1 = Me, R^2, R^3 = 4-[$(CH_2)_2C_6H_4$-*o*]-5	$CDCl_3$ (room temp.): both tautomers are present in nearly equal proportions	93CJC678
R^1 = EtOCO, R^2 = Br, R^3 = Me	DMSO-d_6: **2a** predominates, K_T = 4.0	99H(50)227
	Solid: only **2a**	99H(50)227
R^1 = EtOCO, R^2 = Br, R^3 = Ph	DMSO-d_6: **2a** predominates, K_T = 1.2	99H(50)227
	Solid: only **2a**[h]	99H(50)227

[a] Positions of the substituents are referred to the tautomeric structure **2a.**

[b] A negative value of free energy or energy in quantum chemical calculations corresponds to the tautomer **2a** (3-X tautomer) being more stable than **3a** (5-X tautomer). The equilibrium constant is calculated as K_T = **2a/2b.**

[c] 3(5)-Methylpyrazole is liquid at room temperature.

[d] The host compound is 1,1-bis(2,4-dimethylphenyl)but-2-yn-1-ol (Seebach diol).

[e] With PF_6^- as the counterion.

[f] K_T was calculated from measurements of basicities of *N*-methyl derivatives.

[g] The calculations were performed for the compound in which a methyl group (R^1) was replaced by a hydrogen.

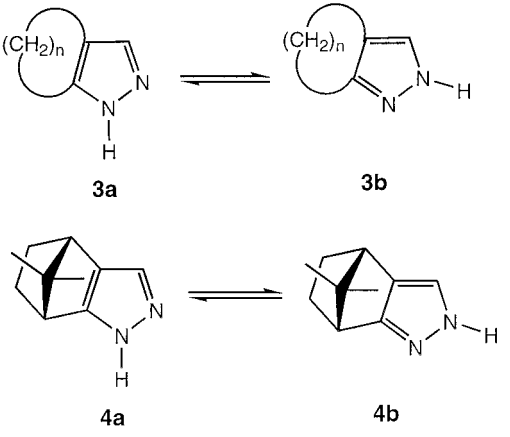
[h] Presents temperature-dependent solid-solid phase transition.

position of the tautomeric equilibrium. A general trend consists in the preferential stabilization of the tautomers **2a** when a π-acceptor group (R^1 = NO_2, N_2^+, Ph, N_3) is in conjugated position with respect to the pyrrole-type nitrogen (79OMR587). In contrast to this trend is, however, the observation that tautomer **2b** (R^1 = EtOCO) is the predominant form (84OMR603) for 3(5)-ethoxycarbonylpyrazoles in DMSO solution; this result was later disproved [99H(50)227]. Strong σ-acceptor substituents (R^1 = NH_3^+, CF_3) in the ring favor the stabilization of type **2b** tautomers. In the solid state, 3(5)-ethoxycarbonylpyrazoles exist exclusively as tautomers **2a** as was established by both X-ray analysis and solid state ^{13}C NMR [99H(50)227].

The alkyl groups (*tert*-butyl > isopropyl > methyl) prefer ring position 5; i.e., tautomer **2a** is energetically favored. A relationship was established (93CJC678) between σ_m-constants of the substituents and the tautomerism of pyrazoles: when σ_m is positive the substituent prefers the 3-position, and when σ_m is negative the substituent prefers the 5-position. In the gas phase (92JOC3938) and in solution, the phenyl group stabilizes the 3-substituted tautomers, whereas the *tert*-butyl substituent prefers the 5-position. In general, the tautomer present in the solid is also the major tautomer in solution.

Special attention has been given to elucidation of the role of the Mills–Nixon effect on the tautomeric equilibria of pyrazoles **2a** $\rightleftharpoons$ **2b** with unsaturated rings annelated at positions 4,5 or containing two bulky substituents R^2, R^3 [93AX(C)724; 94NJC269; 96MC18; 97MI121, 97MI189]. The study of tautomerism was found to be a sensitive indicator of the existence of this ring-strain effect (97MI189, 97T1403), which remains one of the controversial principles of classic structural chemistry [94AG(E)1721]. In accordance with expectations based on the standard version of the Mills–Nixon effect, the tautomeric equilibrium in compounds with small rings fused to the pyrazole unit, **3** (n = 1– 4) should be shifted to tautomer **3b,** i.e., that having the largest single-bond character in the bond shared by both rings (Scheme 3). It was found indeed to be the case for pyrazole **3,** n = 3 (94NJC269) and campho[2,3-*c*]pyrazole **4,** in which case tautomer **4b** predominates in both crystal and solution (see Table I).

Semiempirical AM1 and *ab initio* RHF/6-31G* calculations have been performed (97MI189) on the model pyrazoles **3** (n = 1) and **2,** which also confirmed the energy preference of the type **3b** tautomers. A relationship has been found between ring strain (angles R^2C4C5 and R^3C5N1) and the energy difference between the two tautomeric forms, **2a** and **2b.** An interesting prediction following from these calculations is that the reverse Mills–Nixon effect, i.e., the relative stabilization of the type **2a** tautomer, should be observed for overcrowded pyrazoles **2** with bulky substituents R^2 and R^3, for instance, *t*-butyl or adamantyl groups.



SCHEME 3

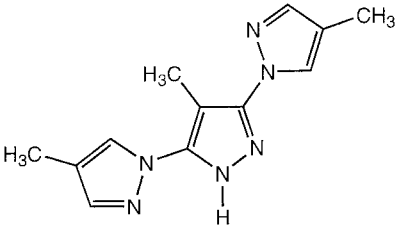
b. *Kinetics of Proton Exchange in Solution.* The relatively narrow range of chemical shifts inherent to ^{1}H NMR spectroscopy often presents problems in slowing the fast proton exchanges in pyrazole-associated species in solution sufficiently to be able to observe separate signals for the individual tautomers. In early studies of the prototropic rearrangement **1a** ⇌ **1b,** their rates were found to be so high that the molecule retained, in ^{1}H NMR terms, their effective C_{2v} symmetry down to the lowest temperature achievable in these experiments. Utilization of HMPT as a solvent helped to freeze the proton transfer enough to observe both degenerate annular tautomers of pyrazole in the ^{1}H NMR spectrum and to estimate the energy barrier to their interconversion, ΔG^*_{289}, as 58.6 kJ mol^{-1} at 0.1–0.2 *M* concentration of the solution (77IZV2390).

The problem has been overcome most reliably by using ^{13}C - or ^{15}N NMR techniques, which provide a wider range of chemical shifts and, thus, allow one to quantitatively characterize many dynamic processes which are too fast to be measured by methods of ^{1}H NMR spectroscopy.

One of the first studies of this type was accomplished by A. Nesmeyanov *et al.* (75T1461, 75T1463), who recorded well-resolved ^{13}C NMR spectra (22.635 MHz) of unsubstituted pyrazole **1** in concentrated (1–2 *M*) solution in an ether/tetrahydrofuran mixture. At –118°C, the spectrum consisted of three separate signals, one for each of the carbon nuclei. The energy barrier estimated at the temperature of coalescence of C-3 and C-5 signals (about −100°C) was equal to 46 kJ mol^{-1}. A significant [although later claimed to be exaggerated (93CJC1443)] decrease in the rate of the exchange reaction was observed for N-deuterated pyrazole, a fact which was explained by the

contribution of tunneling in the mechanism of prototropic tautomerism in pyrazole associates in solution (76CPL184; 77KGS781). Subsequent to the studies of the Russian authors, W. Litchman (79JA545) reported on the kinetic data available from the temperature-induced collapse of the C-3 and C-5 NMR peaks of pyrazole in DMSO-d_6. It was found that the proton exchange in pyrazole is, in fact, slow on the ^{13}C NMR time scale and that the C-3 and C-5 peaks do not coalesce until the temperature is raised to 64°C. The value of the free energy barrier, ΔG^*, was determined to be as high as 61.9 kJ mol^{-1}, which compares well with values obtained for pyrazole (ΔG^* = 63 kJ mol^{-1}) (77JOC659) and 3,5-dimethylpyrazole (77JOC659; 85JA5290) in another dipolar solvent HMPT (ΔG^* = 63 kJ mol^{-1}) and in the solid state (ΔG^* = 57 kJ mol^{-1}) by ^{13}C CPMAS NMR.

Adding small amounts of water to Et_2O/THF [77ZN(C)89] [or even significant ones to DMSO (79JA545)] solutions of pyrazole caused only slight effects on the rate of proton exchange. However, the use of acetone or other solvents resulted in very rapid proton exchange manifested by an average resonance for C-3 and C-5 even at 6°C (74JOC357; 77JOC659; 79JA545). The same effect was achieved by the addition of trace amounts of an acid to pyrazole solutions. This observation led to the conclusion (79JA545) that the cases of rapid proton exchange reported for pyrazole should be attributed to acid impurities present in the samples.



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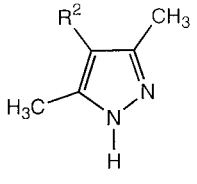
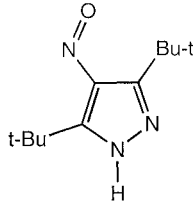
ΔG^* = 49.8 kJ mol^{-1}



6

a) R^2 = Cl, ΔG^* = 53.6kJ mol^{-1}
b) R^2 = NO_2, ΔG^* = 50.6 kJ mol^{-1}



7

Accounting for this effect, it was possible to apply dynamic ^1H NMR spectroscopy to measure energy barriers to the prototropic rearrangements of pyrazoles. Temperature-variable spectra of a series of 4-substituted pyrazoles **5** and **6** have been studied in methanol-d_4 solutions and the free energy barriers of the degenerate type **2a** ⇌ **2b** tautomerization reported (93CJC1443).

The values of ΔG^* correspond to the exchange reaction in N-deuterated pyrazoles **5,6** and are expected to be slightly higher than those for the rearrangements in N-H compounds.

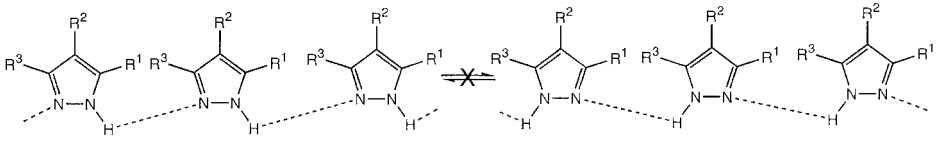
In the case of 3,5-di-*tert*-butyl-4-nitrosopyrazole **7,** the proton exchange reaction due to annular tautomerism observed in CD_2Cl_2 solution is accompanied by a second dynamic process of restricted N=O rotation [97JCS(P2)721]. By comparison with the spectral behavior of the *N*-methyl derivative of **7,** it was found that the broadening and then splitting of the *tert*-butyl signals observed at cooling the solution to −80°C should be primarily attributed to slowing down the proton exchange reaction. Traces of acids accelerate this process.

A notable result of the studies of kinetics of proton exchange occurring in pyrazole solutions is the high negative value of the entropy of activation: $\Delta S^* = -105$ J deg^{-1} in DMSO (79JA545). Such a value points to the complexity of the process rather than to the simple ionization reaction facilitated by a solvent [see (89PAC699)]. The most important contribution to understanding of the mechanisms of proton exchange in pyrazole and its derivatives has been made by the use of methods of high-resolution solid-state NMR spectroscopy.

c. *Structure and Annular Tautomerism of Pyrazoles in the Solid State.* The development of the methods of high-resolution solid-state NMR spectroscopy: (1) ^{13}C NMR spectroscopy under conditions of ^{1}H-^{13}C cross-polarization (CP), (2) ^{1}H decoupling, and (3) magic angle spinning (MAS) (82ACR208), had a profound impact on the study of azole tautomerism. These methods allow one to detect unambiguously whether dynamic processes occur in a solid at the molecular level as solid-state reactions. In parallel with the X-ray structural analyses, the temperature variable multinuclear NMR CPMAS experiments have provided a deep insight into the structure of the molecular networks undergoing dynamic transformations and kinetic parameters of the such processes.

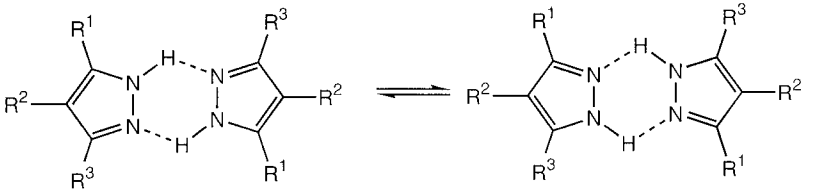
X-Ray crystallography investigations [85JA5290; 89JA7304; 92JA9657; 94AX(B)746, 94JCS(CC)1143, 94JHC695; 95JOC1965; 97JCS(P2)101, 97JCS(P2)1867; 99AX(B)441] revealed that N-unsubstituted pyrazoles in the solid state form linear oligomers (catemers) **8,** cyclic dimers **9,** trimers **10,** or tetramers **11,** depending on the substituents in the ring (Schemes 4–6). For type **2** pyrazoles with $R^1 \neq R^3$, four situations are possible in the solid state: (1) the most common is that where only one tautomer is present in the crystal and only one kind of crystal can be obtained; (2) both tautomers are present in the same crystal; (3) two, or even more, polymorphs of the same tautomer can be isolated; and (4) each tautomer crystallizes in a different crystal type (desmotropy). The rather rare latter situation is represented by compounds **9e** and **10c** (Scheme 5) [94JCS(CC)1143].

The first observation of the proton transfer in pyrazoles in the solid state was made for the intermolecular tautomerism in 3,5-dimethylpyrazole **10b** (85JA5290). The degenerate rearrangement was recorded using the

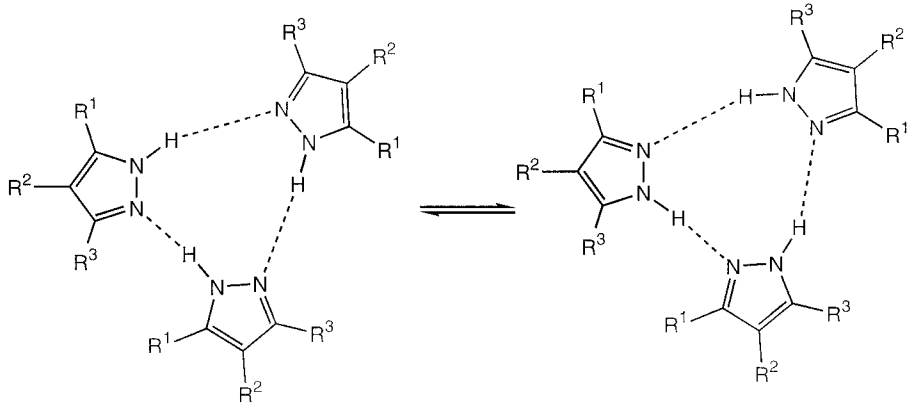


8: a) $R^1 = R^2 = H$; b) $R^1 = R^3 = Me$, $R^2 = Br$; c) $R^1 = R^3 = Me$, $R^2 = NO_2$;
d) $R^1 = N_3$, $R^2 = Ph$, $R^3 = H$; e) $R^1 = Ad$, $R^2 = R^3 = H$; f) $R^2 = Ad$, $R^1 = R^3 = H$

SCHEME 4

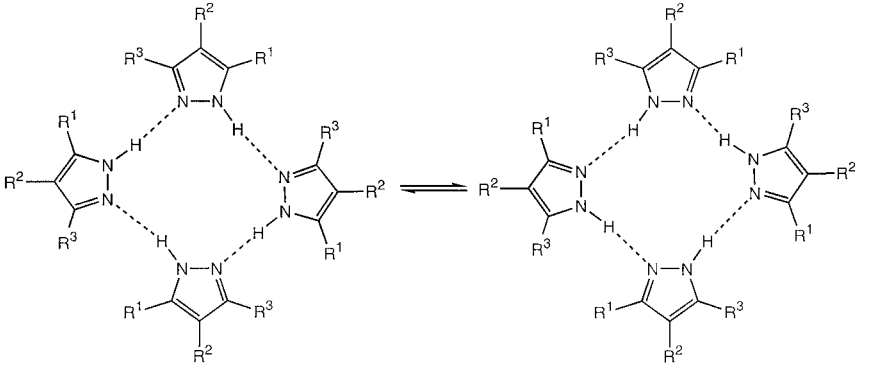


9: a) $R^1 = R^3 = Ph$, $R^2 = Br$; b) $R^1 = R^3 = t$-Bu, $R^2 = H$; c) $R^1 = R^3 = t$-Bu, $R^2 = NO_2$;
d) $R^1 = R^3 = Ph$, $R^2 = NO_2$; e) $R^1 = Me$, $R^2 = NO_2$, $R^3 = H$.



10: a) $R^1 = R^3 = H$, $R^2 = NO_2$; b) $R^1 = R^3 = Me$, $R^2 = H$; c) $R^1 = H$, $R^2 = NO_2$, $R^3 = Me$;
d) $R^1 = Ph$, $R^2 = Br$, $R^3 = H$; e) $R^2R^3 = [(CH_2)_2CH(CH_3)CH_2]$

SCHEME 5



11: a) $R^1 = R^3 = Ph$, $R^2 = H$; b) $R^1 = Ph(Me)$, $R^2 = H$, $R^3 = Me(Ph)$.

SCHEME 6

^{13}C CPMAS NMR method; the energy barrier to a triple-proton migration in the cyclic trimer ($\Delta G^* = 57$ kJ mol^{-1}) was close to that in solution (Table I). An even lower value of about 39 kJ mol^{-1} has been recently reported for the proton transfers in the solid state of 3,5-dimethyl-4-adamantylpyrazole and 3,5-diadamantylpyrazole [97JCS(P2)1867]. These compounds are expected to be cyclic hydrogen-bonded structures, dimers, or trimers. Slow prototropic exchange in 4-undecylpyrazole in the solid state was studied using ^{13}C CPMAS NMR spectroscopy (95HCO157). As revealed by both the experimental results obtained and semiempirical calculations (AM1 and PM3 methods), this compound exists as a mixture of tautomeric cyclic trimers **10** ($R^1 = R^3 = H, R^2 = n\text{-}C_{11}H_{23}$). A very detailed study of the mechanism and energetics of this solid state tautomeric rearrangement in pyrazoles was based on a combined application of ^{13}C and ^{15}N CPMAS NMR spectroscopy, ^{14}N quadrupole double resonance, and X-ray diffraction techniques (89JA7304; 96JMR46). It was proved unambiguously that a temperature-dependent process (hydrogen disorder) observed in crystalline 3,5-dimethylpyrazole indeed corresponds to a solid-state proton transfer reaction and not to correlated 180° rotations of the pyrazole molecules. The combination of the three magnetic resonance methods made it possible to study the dynamics of the solid-state tautomerization over a broad temperature range between 100 and 338 K and assign it to a correlated three-proton jump within the hydrogen-bond network of the trimer **10b.**

After these findings, evidence was presented that pyrazoles which crystallize as cyclic dimers **9a/9b** and tetramers **11a** are subject to double and quadruple proton transfers respectively (92JA9657; 95JOC1965). An im-

portant feature of the kinetic results on the proton transfers in the associates **9–11** is the very large kinetic isotope effects, especially for the trimer. These values, presented in Table II along with other kinetic parameters, are much larger than those observed for pyrazoles in liquid solution (76CPL184). Also, the values of 10^{11}–10^{12} s^{-1} found for the frequency factors are in contrast to a large negative activation entropy ($\Delta S^* = -104.6$ J mol^{-1}) calculated for pyrazole exchange in DMSO solution (89JA7304). These findings witness that the mechanisms of proton migration in the solid and the liquid states are different. From the data of Table II one can see that the rates of proton transfer in cyclic associates first decrease when passing from dimers to trimers and then increase as the number of protons transferred increases in tetramers. This effect was explained as arising from a switch from a concerted reaction pathway to a stepwise reaction pathway (92JA9657). The isotopic effects (Table II) are in accord with this explanation, suggesting that in the case of dimer **9a** and trimer **10b** two and three protons respectively are involved concertedly in the rate-limiting step. For the tetramer **11a,** the smaller isotope effects are in line with a stepwise mechanism, with two protons migrating in each step.

When methyl groups in 3,5-dimethylpyrazole **10b,** trimeric in the solid, were changed for *tert*-butyl groups, three types of dimers **9b** differing in the conformations of the *tert*-butyl groups were obtained. The tautomerism takes place in only one of these conformers, which preserves a symmetry plane in the crystal. Variable-temperature ^{15}N CPMAS NMR spectroscopy indicated a value of 56.6 kJ mol^{-1} as the activation energy of the process (95JOC1965). A singular case of the influence of polymorphism on the proton exchange is exemplified by tetrameric 3(5)-methyl-5(3)-phenylpyrazole

TABLE II

KINETICS OF THE MULTIPLE-PROTON TRANSFER IN CYCLIC ASSOCIATES OF PYRAZOLES [89JA7304, 97JCS(P2)101]

Compound	Isotopic composition	log A	E_a, kJ mol^{-1}	k/s^{-1} (330 K)	$k^{(H)_n}/k^{(D)_n}$	Contribution $\sqrt[n]{k^{(H)_n}/k^{(D)_n}}$
9a, dimer	HH	11.4	44.4	6400	k^{HH}/k ca.25	5
	DH	11.8	48.5			
	DD	13.4	63.2			
10b, trimer	HHH	11.8	50.6	1000	k^{HHH}/k^{DD} ca.50	3.68
	DHH	11.8	54.0			
	DDH	12.0	58.2			
	DDD	11.8	59.8			
11a, tetramer	HHHH	11.8	44.4	11300	k^{HHHH}/k^{DDDD} ca.12	1.86
	DDDD	13.8	61.9			

11b (95JHC451). A polymorph formed by a mixture of both tautomers was found to be susceptible to tautomeric rearrangement (E_a = 47.0 kJ mol^{-1}), whereas another polymorph formed exclusively by 3-phenyl-5-methyl tautomer was dynamically inactive. Recently an example of the NH proton transfer occurring in the solid state in a tautomeric mixture of pyrazoles **10e** with an equilibrium constant different from 1 has been described (97MI121).

No proton transfers were observed in linear oligomers (catemers) of pyrazoles **8** in the solid, a fact which was understandable because such rearrangements would require a very high activation energy [97JCS(P2)101]. A possible exception to this rule is a catemer **8f,** for which slow proton transfer was observed in the solid state [97JCS(P2)1867].

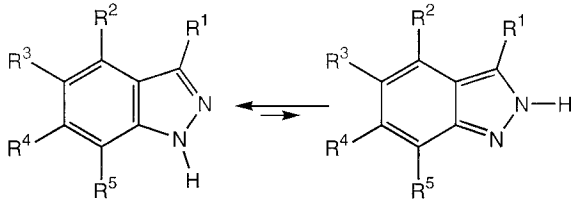
d. *Theoretical Study of the Proton-Transfer Reaction Pathways.* *Ab initio* quantum mechanical calculations aimed at modeling both concerted and stepwise mechanisms for the proton transfer in the cyclic associates of pyrazoles have been performed at various levels of approximation including the use of double-zeta and split-valence basis sets with the addition of polarization functions and with electron correlation and corrections for BSSE taken into account [97JCS(P2)101].

Dimer **9,** $R^1 = R^2 = R^3 = H$, trimer **10,** $R^1 = R^2 = R^3 = H$, and tetramer **11,** $R^1 = R^2 = R^3 = H$, with the geometries derived from experimental X-ray structures of the relevant pyrazoles, were chosen as the appropriate model systems. Although no full geometry optimization for the structures along the reaction paths was applied due to the complexity of the interconverting molecular systems and no rigorous identification of all the calculated stationary points was accomplished, the main results were in accord with the experimental findings of an energy preference for concerted two- and three-proton migrations in dimeric and trimeric associates. For the tetramer, the calculation predicted the stepwise mechanism.

Further insight into detailed mechanisms of the proton transfers leading to tautomerization within the network of hydrogen bonds in the associates of pyrazoles may be achieved through more accurate accounting for geometry relaxation in the course of the rearrangement. This requirement is known to be of primary importance for both the correct estimation of energy barriers to multiple cooperative proton migration in various hydrogen bond associates and the selection of energetically preferable (concerted or nonconcerted) mechanisms (91JA1596; 96IZV817; 97JA12223).

2. *Indazole and Its Derivatives*

The data obtained from all the various physicochemical methods point to the predominance of the 1*H* tautomer **12a** in the prototropic equilibrium over its 2*H* counterpart (Scheme 7).



R^1, R^2, R^3, R^4 = H, Me, *t*-Bu, Cl, Br, I, NH_2, NO_2, N_3, OMe, OH, Ph

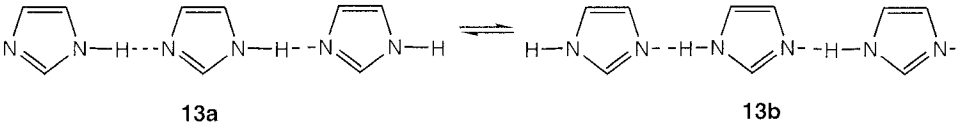
SCHEME 7

The structure of indazoles in solution was thoroughly studied with the use of NMR spectroscopy. Information available on the ^{13}C NMR spectroscopy of indazoles was collected and systematized in (95KGS1159), whereas that related to ^{15}N NMR spectroscopy appeared in (97MRC35). Neither the type of substitution nor the solvent employed for recording the spectra affect the conclusion on the significant predominance of the 1*H* tautomer over the 2*H* form. This phenomenon is well explained by low aromaticity in the latter [91H127; 93AHC(56)303; 96JCS(P2)57]. For indazole **12** $R^1 = R^2 = R^3 = R^4 = R^5 = H$ itself, the tautomeric equilibrium constant in water solution is K_T = **12a/12b** = 51.4 (ΔG^0_{25} = 9.6 kJ mol^{-1}) (94JPC10606). In the gas phase, the energy preference of the 1*H* tautomer is even greater as was confirmed by photoelectron (78JST33, 78JST203) and microwave spectroscopy (92JSP1). Solvation by water more effectively stabilizes the 2*H* tautomer as confirmed by *ab initio* RHF/6-31G [88JST(T)115, 94JPC10606] calculations. At this level of approximation, the 1*H* tautomer was found to be intrinsically more stable than the 2*H* form by approximately 41 kJ mol^{-1}. More accurate MP2/6-31G* calculations [96JCS(P2)57] reduce this difference to 15.1 kJ mol^{-1}. The addition of the thermal energy correction and entropy effects led to the value of ΔG^0_{25} = 17.2 kJ mol^{-1}. Only the 1*H* tautomers exist in the solid state for indazole, benzo[*g*]indazole and 3-methylbenzo[*g*]indazole according to ^{13}C CPMAS NMR experiments (83H1713; 93CJC678) and X-ray analysis (74T2903).

3. *Imidazole, Benzimidazole, and Their Derivatives*

In solution and in the solid state, imidazole and its N2-unsubstituted derivatives form large hydrogen-bonded associates **13** (Scheme 8) [76AHC(S1), p. 266; 84CHEC-I(5)345, 84JPC5882; 96CHEC-II(3)77; 97JST(415)187].

Due to the perfect linear arrangement of the N-H···N hydrogen bridges in **13,** extremely fast cooperative proton transfers occur in solution which



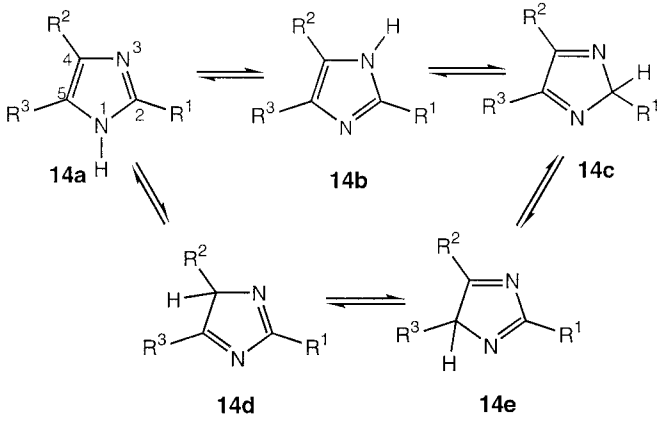
13a **13b**

SCHEME 8

lead to averaging of the positions 4 and 5 in the ring on the NMR time scale. In contrast with pyrazoles, only averaged ^{1}H, ^{13}C, and ^{15}N NMR spectra of effective C_{2v} symmetry were recorded so far for imidazole, benzimidazole, and many of their derivatives [75T1461, 82JOC5132, 96CHEC-II(3)77, 97MRC35]. Slow prototropic annular tautomerism of 2-perfluoroalkylimidazoles was attributed to intramolecular N-H···F bonds realized in these compounds (82JOC2867; 95OPP33). The proton exchange reaction is subject to general and specific acid and base catalysis [76AHC(S1), p. 266; 87AHC(41)187].

As in the case of pyrazole, relative energies of nonaromatic 2*H* **14c** and 4 (or 5) **14d,e** ($R^1 = R^2 = R^3 = H$) isomers of imidazole are too high for them to contribute to the tautomeric equilibrium (Scheme 9). According to STO-3G calculations (86BSF429) these values are equal to 60.4 and 67.7 kJ mol^{-1} respectively relative to **14a,b** ($R^1 = R^2 = R^3 = H$).

A major part of the information available on positions of tautomeric equilibria **14a** ⇌ **14b** of imidazoles stems from the basicity measurements of the N-unsubstituted imidazoles and N-methylated derivatives of tautomers **14a** and **14b.** The data obtained in earlier [76AHC(S1), p. 272] and more recent [96CHEC-II(3)77] studies are collected in Table III. These are generally in line with those obtained by the use of ^{1}H and ^{13}C NMR



14a **14b** **14c** **14d** **14e**

SCHEME 9

TABLE III
EQUILIBRIUM CONSTANTS (K_T = **14a/14b**) FOR IMIDAZOLE ANNULAR TAUTOMERISM AS DETERMINED FROM pK_a MEASUREMENTS

Compound[a]	K_T	Reference
4-CH_3	1.1	96CHEC-II(3)77
4-Ph	10-37	76AHC(S1), p. 278
4-NO_2	320-500	76AHC(S1), p. 278
4-Cl	90	96CHEC-II(3)77
4-Br	47	96CHEC-II(3)77
4-I	19	96CHEC-II(3)77
2-Br-4-NO_2	210	76AHC(S1), p. 278
4-NO_2-5-Cl	118	76AHC(S1), p. 278
2,4-$(NO_2)_2$	1.1-3.1	76AHC(S1), p. 278

[a] Position of substituents is indicated according to the structure **14a.**

[79JOC3864; 83T3797; 86JHC921; 92JCS(P1)2779; 98JCS(P2)1665], ^{15}N NMR (79JOC3864; 83HCA1537) and UV-spectral (86ZC378) methods.

The main conclusion on the influence of substituents in the imidazole ring on the state of the tautomeric equilibria **14a** ⇌ **14b** is that electron-withdrawing groups favor the 4-position, i.e., the tautomers **14a** with R^2 = Hal, NO_2, and so on, are the energetically preferable species. Application of Charton's equation, K_T = [4-R Im]/[5-R Im] = 3.2 σ_m, was discussed in detail [76AHC(S1); 96CHEC-II(3)77]. The equation was found to be in a qualitative agreement with the experimental data presented in Table III.

Theoretical studies of the relative stabilities of tautomers **14a** and **14b** were carried out mostly at the semiempirical level. AM1 and PM3 calculations [98JST(T)249] of the relative stabilities carried out for a series of 4(5)-substituted imidazoles **14** (R^3 = H, R^2 = H, CH_3, OH, F, NO_2, Ph) are mostly in accord with the conclusion based on the Charton's equation. From the comparison of the electronic spectra of 4(5)-phenylimidazole **14** (R^2 = Ph, R^1 = R^3 = H) and 2,4(5)-diphenylimidazole **14** (R^1 = R^2 = Ph, R^3 = H) in ethanol with those calculated by using π-electron PPP method for each of the tautomeric forms, it follows that calculations for type **14a** tautomers match the experimentally observed spectra better (86ZC378). The AM1 calculations [92JCS(P1)2779] of enthalpies of formation of 4(5)-aminoimidazole **14** (R^2 = NH_2, R^1 = R^3 = H) and 4(5)-nitroimidazole **14** (R^2 = NO_2, R^1 = R^3 = H) point to tautomers **14a** and **14b** respectively as being energetically preferred in the gas phase. Both predictions are in disagreement with expectations based on Charton's equation and the data related to basicity measurements (Table III). These inconsistencies may be

explained by the fact that tautomers **14b** of 4(5)-aminoimidazole and **14a** of 4(5)-nitroimidazole possess higher values of dipole moments compared to their more stable gas-phase tautomers. Accounting for the solvation energy should bridge the intrinsic energy gap.

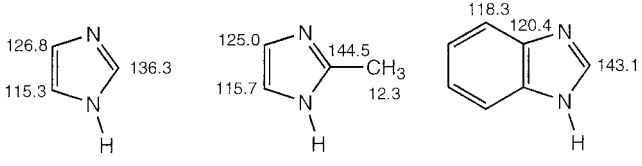
Arguing that the MNDO method is more suitable than the AM1 method for predicting the heats of formation of five-membered nitrogenated aromatic rings, García and Vilarrasa (88H1803) calculated that 4-fluoroimidazole **14a** (R^2 = F, R^1 = R^3 = H) is 2.5 kJ mol^{-1} more stable than its tautomer **14b,** whereas 2,4-difluoroimidazole **14a** (R^1 = R^2 = F, R^3 = H) is 2.1 kJ mol^{-1} less stable than **14b.** The energy differences are very small and disappear when the correction terms related to the lone-pair repulsions between the vicinal pyridinelike nitrogens and fluorine substituents are taken into account.

A theoretical *ab initio* study of the gas-phase basicities of methyldiazoles (90JA1303) included a discussion of the 4(5)-methylimidazole tautomerism. The RHF/4-31G calculations led to the conclusion that the 4-methyl tautomeric form **14a** (R^2 = Me, R^1 = R^3 = H) is 5.2 kJ mol^{-1} more stable than its 5-methyl counterpart **14b.** It was emphasized that this result is to be considered as basic-set dependent. However, a recent theoretical study [94JST(T)45] showed that, starting from the RHF/6-31G* level, all the more accurate approximations indicate a higher intrinsic stability for the 4-methyl tautomer. At the MP2/6-31G* level, the total energy of the 4-methyl tautomer is 0.7 kJ mol^{-1} lower than that of the 5-methyl tautomer. Inclusion of solvation effects can, thus, strongly affect the position of the tautomeric equilibrium **14a** $\rightleftharpoons$ **14b.** Recently, a systematic theoretical study aimed at evaluating the molecular properties and tautomeric equilibrium of 4- and 5-methylimidazoles has been performed [98JST(T)197]. The K_T value for the gas-phase equilibrium was found to be rather sensitive to both basis set and correlation effects. To achieve good agreement with experimental data the use of extended basis sets (6-31+G*, 6-311+G*, and 6-31++G**) at MP2 and DFT levels is required.

Not much information has been added in recent years to the earlier studies of tautomeric equilibria of benzimidazoles based on basicity measurements [76AHC(S1), p. 292]. For 5(6)- and 4(7)-substituted benzimidazoles and 2-methyl-5(6)-substituted benzimidazoles K_T values are very close to 1, which indicates near equivalence in the stability of N1(H) and N3(H) tautomers. The tautomeric equilibria of 2-substituted (H, NH_2, OMe, CN) 5-nitrobenzimidazoles and 4-nitrobenzimidazoles were analyzed with the use of semiempirical MINDO/3 and INDO methods. It was predicted that electron-releasing groups in position 2 shifted the equilibria to the 6-NO_2 and 4-NO_2 tautomers, respectively.

As mentioned, the frequencies of proton jumps leading to establishment of the equilibrium **14a** $\rightleftharpoons$ **14b** in solutions of imidazoles and benzimidazoles

are too high for these forms to be observed on the NMR time scale with ^{13}C [the chemical-shift differences for C4 and C5 in *N*-alkyl derivatives are about 10 ppm (88MRC134)] and even with ^{15}N NMR wherein the nitrogen resonances of the pyrrolelike and pyridinelike nitrogens have chemical-shift differences up to 100 ppm (97MRC35). This indicates that the average lifetime of an individual tautomer before its prototropic rearrangement is about 10^{-4}–10^{-5} s. This rearrangement is frozen in the solid state. Well-resolved solid-state ^{13}C CPMAS NMR spectra were recorded for imidazole [81JA6011, 81JCS(CC)1207], 2-methylimidazole [87H(26)333], benzimidazole [83H1713; 96CHEC-II(3)77], and 2,2′-bis-1*H*-imidazole [96CHEC-II(3)77]: the C(4) and C(5) signals were assigned by comparison with the spectra of the corresponding *N*-methyl derivatives. Recently, an ^1H and ^{13}C NMR spectroscopic study of 2,2′-bisbenzimidazolyl has been performed in DMSO solution in a range of temperatures between 293 and 383 K and an activation energy of 67−69 kJ mol^{-1} was estimated for the proton-transfer process [98JPOC411]. This value falls in the range of those characteristic for tautomerization of other cyclic oxalamidines (89JA5946; 94JA1230), which implies a possibility of a two-step intermolecular mechanism of the tautomeric rearrangement.



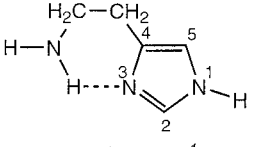
The ^{15}N NMR spectrum of solid imidazole shows two separate signals for the NH (−210 ppm) and the pyridinelike (−138 ppm) nitrogen, indicating that proton exchange is retarded in the solid state (82JA1192). Taking into consideration the very large difference between the ^{15}N chemical shifts of the two nitrogens in imidazole ring, ^{15}N NMR spectroscopy may be regarded as the most accurate and reliable approach for the determination of the K_T values for the tautomeric equilibria **14a** ⇌ **14b** (82JA3945).

Mole fractions of tautomers **14a** (X_a) and **14b** (X_b) can be calculated using the equation

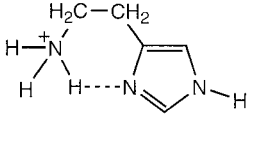
$$P_{obs} = X_a P_a + X_b P_b,$$

where P_{obs} is an observed averaged chemical shift (or coupling constant) and P_a and P_b are chemical shifts (or coupling constants) of pyrrolelike and pyridinelike nitrogens in **14** under the condition of slow proton exchange (e.g., in solid) or in its NMe derivative. The procedure is not highly accurate because uncertainty always exists about how well the model values match

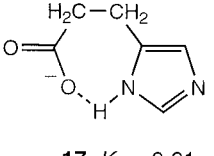
those of the individual tautomers; however, it is generally considered (80JA2881; 82JA3945, 82JOC5132; 93JA6813) as more accurate than that based on basicity measurements. Using averaged values of the ^{15}N chemical shifts of N1 and N3 nitrogens of histamine **15** and a series of its analogs with ability to form a cyclic hydrogen bond within a particular tautomer, Roberts *et al.* (82JA3945) calculated K_T values for the pH range that corresponds to existence of the compounds **15–21** in aqueous solution in the form subject to N1(H) ⇌ N3(H) tautomeric equilibria.[1]



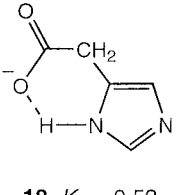
15, $K_T = 0.60$[1]



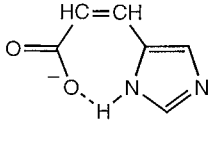
16, $K_T = 0.26$



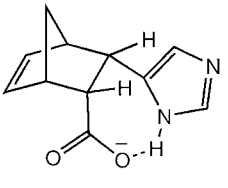
17, $K_T = 0.61$



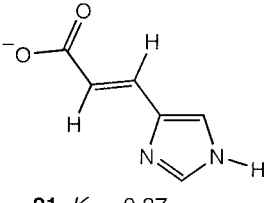
18, $K_T = 0.53$



19, $K_T = 5.2$



20, $K_T = 1.5$

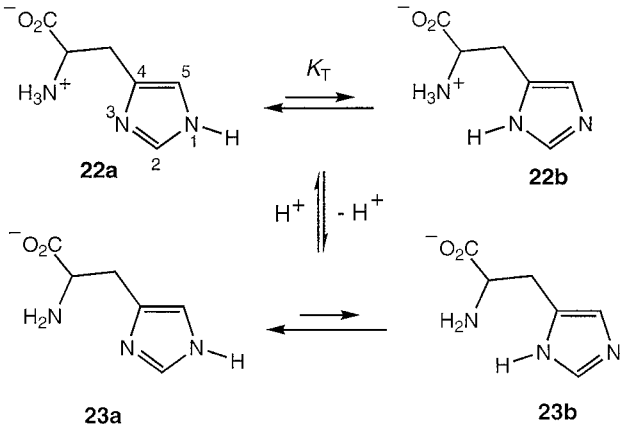


21, $K_T = 0.37$

As seen from the values of K_T, the effect of the cyclic hydrogen bonds in compounds **15, 17,** and **18** is not strong enough to shift the tautomeric equilibria to the N3(H) side. This fact was assigned to the unfavorable eclipsing of methylene groups in the side-chain and to water competing with the side-chain group for formation of a hydrogen bond with an N-H group. Elimination of the first factor in *cis*-urocanic acid **19** and **20** resulted in marked stabilization of the N(3)H tautomers, as confirmed by pK_a measurements [98JCS(P2)1665].

Special attention has been given to the study of tautomeric equilibria in solutions of histidine **22** because the key functional role of such equilibria in proteins is recognized. In aqueous solutions the tautomers of histidine rapidly interconvert and only a single averaged signal is observed for each ring nitrogen (Scheme 10).

[1] The K_T = [N3(H)]/[N1(H)] values were calculated with use of 83 ppm ^{15}N chemical shift difference for N1 and N3. The values K_T based on calculations for averaged N1 shifts are given. For all the structures numbering the ring atoms is as given in formula **15.**

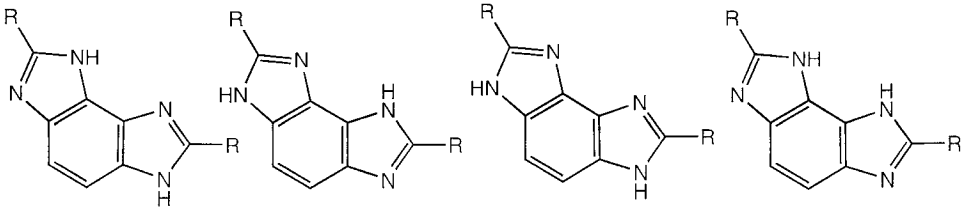


SCHEME 10

In earlier studies, values for these ^{15}N chemical shifts were estimated from model N-methylated compounds (78JA8041; 80JA2881; 82JA3945) or from ^{15}N NMR spectroscopy of the tautomeric forms of histidine in the solid state where tautomeric exchange is slow (82JA1192). The use of 80% ethanol/water as solvent allowed Bachovchin *et al.* (93JA6813) to observe directly the individual tautomeric forms of histidine in ^{15}N NMR spectra at $-55°C$. The solvent was found to show a little effect on the intrinsic ^{15}N shifts of the individual tautomers and the tautomeric equilibria of the imidazole ring. In the pH interval where the imidazole ring is neutral, three of the four possible forms of histidine were observed in ^{15}N NMR spectra at $-55°C$. Only **22b** was not directly detected. Noteworthy is that only forms **22a** and **23a** were observed in the ^{15}N NMR solid-state spectra of histidine (82JA1192). The mole fraction of the tautomeric form **22b** calculated from ^{15}N chemical shifts in solutions at pH ~8.2 where zwitterion **22** predominates is 0.18. This value agrees well with earlier estimates (80JA2881) based on the values of the $^2J_{NH}$ coupling constants. Stabilization of **22a** over **22b** is apparently caused by formation of a hydrogen bond with participation of the N3 center. At pHs higher than 9.2, where deprotonation of the α-amino group does not donate a hydrogen bond to the N3 center, tautomer **23a** still remains the energetically preferable form. The mole fraction was estimated to be 0.35 (93JA6813). Recently an efficient method for determining the protonated and deprotonated forms and the tautomeric states of histidine residues, even in large-molecular-weight proteins (up to 30–40 kDa), has been developed based on measurements of coupling constants between ^{15}N and ^{13}C in the imidazole ring (98JA10998). In all histidine-containing proteins the **22a** and **23a** type tautomeric forms were found to be dominant.

Tautomeric equilibria between two degenerate pairs (**A', A"** $\rightleftharpoons$ **B', B"**)

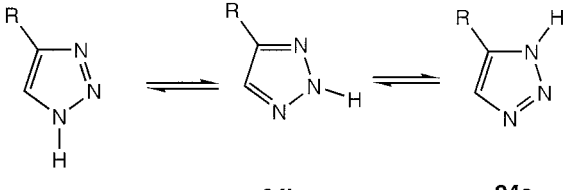
were observed in low-concentration DMSO-d_6 solutions of benzodiimidazoles, bearing similar substituents in the both imidazole rings [98H(48)113]. In these equilibria, the unsymmetrical tautomers **A'** and **A″** predominate.



4. *1,2,3-Triazoles and Benzotriazoles*

Annular prototropic tautomerism of 1,2,3-triazole (*v*-triazole) and its C-substituted derivatives involves the equilibrium of three possible isomers **24a**–**24c.** In the case of the parent compound (R = H), **24a** and **24c** are degenerate isomers (Scheme 11).

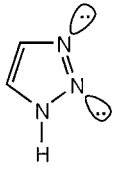
In the gas phase, the symmetrical 2*H* tautomer of 1,2,3-triazole **24b** (R = H) dominates in the equilibrium mixture as proved by mass (73OMS271), IR (96LA1041), and microwave spectroscopy; electron gas diffraction [88ACS(A)500]; gas-phase dipole moment (91JPC3119); photoelectron spectroscopy [81ZN(A)1246; 87CP249]; and ICR gas-phase basicities (89JCC426) studies. This conclusion is in accord with the results of most theoretical calculations, including RHF/6-31G*//6-31G* (ΔE = −20.5 kJ mol^{-1}) (89JA7348), MP2/6-31G**//3-21G (ΔE = −19.8 kJ mol^{-1}) (90JPC5499) and MP2/6-31G*//6-31G* (ΔE = −21 kJ mol^{-1}) (91JPC3119; 95JPC12790) levels of approximation [see also 76AHC(S1), p. 281; 94JOC2799; 95ZOR1422; 96CHEC-II(4)1; 98KGS645 for detailed reviews of theoretical studies with the use of less sophisticated *ab initio* and semi-empirical (CNDO/2, MNDO, AM1, PM3) methods].



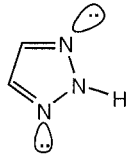
SCHEME 11

The crystal structure analysis of the parent 1,2,3-triazole in the solid state unambiguously demonstrated that it crystallizes as a 1:1 molecular complex of both possible tautomers **24a** and **24b,** linked by a N-H···N hydrogen bond [97AX(C)1846].

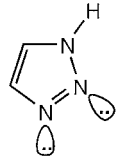
In solution, 1*H* tautomer **24a** (R = H) is the most stable species because of its much larger dipole moment (according to MP2/6-31G* calculations (95JPC12790) the values of dipole moments of 1*H* and 2*H* tautomers of 1,2,3-triazole are correspondingly 4.66 D and 0.06 D; experimental values for the gas phase are 4.38 D and 0.22 D [88ACS(A)500; 91JPC3119]), which leads to the better solvation of **24a** (R = H) in all usual solvents. In the ^{15}N NMR spectra of **24** (R = H) in $CDCl_3$ and DMSO solutions, two different exchange averaged nitrogen resonances are observed. Using the values of the ^{15}N chemical shifts for the *N*-methyl derivatives of **24a** and **24b** and allowing for the degeneracy of the 1*H* tautomer, the mole fractions of **24b** were calculated as 0.34 in $CDCl_3$ and 0.55 in DMSO (82JOC5132). According to ^1H NMR studies, both 1*H* and 2*H* tautomers are present in CD_2Cl_2 solution, their relative ratio depending upon concentration [84JCS(P2)1025]. Basicity measurement evidence confirms that the 2*H* tautomer is favored in aqueous solution by a factor of two [89JCS(P2)1903].



24a



24b



24c

The energy preference for the 2*H* tautomer of 1,2,3-triazole **24b,c** (R = H) over the 1*H* species **24a** (R = H) was rationalized in terms of a significant destabilizing factor inherent in polyazaheterocycles with adjacent sp^2 nitrogens (86JA3237). Lone-pair repulsion in **24a** is larger than that in **24b** and leads to energetical preference of the latter, all other factors being approximately equal for these species.

Little is known about the influence of *C*-substituents on the position of the annular tautomeric equilibrium **24a** ⇌ **24b** ⇌ **24c.** According to MNDO calculations (88H1803), **24a** is the energetically preferable form for the case of R = F and also for 4,5-difluoro-1,2,3-triazole. Another C(4)C(5)-disubstituted 1,2,3-triazole, 5(4)-amino-1,2,3-triazole-4(5)-carboxamide, crystallizes exclusively as a 5-amino-1*H* tautomer [74JCS(P2)1849].

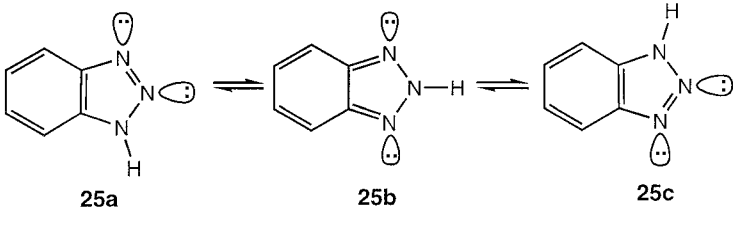
As an ^1H and ^{13}C NMR study (78OMR578) showed, in DMF solution at

−55°C, 4(5)-vinyl-1,2,3-triazole **24** (R = CH=CH_2) forms a mixture of all three possible tautomers. At equilibrium the 2*H* tautomer **24b** predominates (70%) and the 1*H* **24a** and 3*H* **24c** occur in amounts of 20 and 10%, respectively.

In benzotriazole **25,** annelation of a benzene ring to the 1,2,3-triazole moiety requires careful consideration of another important effect that contributes to the stability of annular tautomers of azoles, i.e., aromaticity. According to X-ray crystallography [74AX(B)1490, 74T2903], ^{13}C NMR (83H1713), and ^{15}N NMR (94JST321; 97MRC35) CPMAS spectroscopy only the 1*H* tautomer of benzotriazole **25a,c** is present in the solid state (Scheme 12).

In solution, benzotriazole also exists almost exclusively as the 1*H* tautomer **25a,c.** This conclusion was drawn on the basis of early ^{1}H NMR [69T4667; 76AHC(S1), p. 295] and ^{15}N NMR (82JOC5132; 97MRC35) spectral studies and confirmed by measurements of enthalpies of solution, vaporization, sublimation, and solvation in water, methanol, and DMSO (89JA7348).

The conventional explanation for the observed shift of the tautomerism of benzotriazole toward the 1*H* form, which is unfavorable under all conditions in the case of parent 1,2,3-triazole **24,** is based on the partial lack of aromaticity in the 2*H* tautomer **25b** [91H127; 93AHC(56)303; 95ZOR1422]. The difference in aromaticity of the two forms was estimated as 39.7 kJ mol^{-1} (89JA7348). This effect was considered [76AHC(S1), p. 295; 89JA7348; 96CHEC-II(4)1] as exceeding the contribution of the unfavorable lone-pair repulsion effect. Such a conclusion on the relative stability of the tautomers of benzotriazole was in line with the results of semiempirical (MNDO, AM1, PM3) and *ab initio* calculations without accounting for electron correlation (89JA7348; 90JOC5683). For instance, in a RHF/6-31G approximation the difference in total energy of the tautomers **25a** and **25b** (R = H) amounts to 20.1 kJ mol^{-1} (89JA7348). The results of mass spectroscopy (73OMS1267) and microwave spectroscopy [93JSP(158)399, 93JSP(161)136] studies as well as those of fluorescence excitation and emission spectroscopy of jet-cooled benzotriazole (93CP325) were also dis-



SCHEME 12

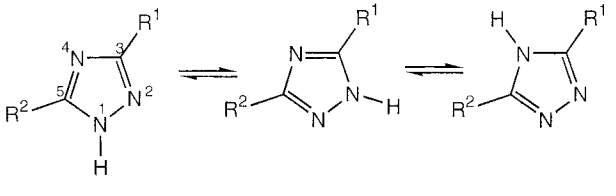
cussed assuming the 1*H* tautomer **25a,c** as the only species observed in the gas phase. Recently, however, the spectroscopic data were interpreted in terms of a mixture in the gas phase of both tautomers, which depends on temperature (94JOC2799). By studying the UV spectra of benzotriazole in the gas phase at three temperatures, Catalán *et al.* (93JOC5276) concluded that the 2*H* tautomer was the dominant tautomeric form, which is about 17 kJ mol^{-1} more stable than the 1*H* form. This unexpected result can be reproduced by theoretical calculations provided electron correlation is taken into account simultaneously with full geometry optimization. At least the MP2/6-31G** level of approximation is required to describe correctly the delicate energy balance between the repulsion of the adjacent lone pairs of the 1*H* tautomer and its larger aromatic stabilization with regard to the quinonoid 2*H* tautomer (94JST321). At this level, the energy difference between the tautomers was found to be 10.6 kJ mol^{-1}.

Attempts were undertaken to evaluate the rates of proton exchanges **24a** ⇌ **24b** ⇌ **24c** and **25a** ⇌ **25b** ⇌ **25c** in solutions of 1,2,3-triazole and benzotriazole. Based on variable-temperature ^{1}H NMR spectroscopy, the intramolecular mechanism corresponding to a 1,2-prototropic shift was suggested [84JCS(P2)1025] for the annular tautomerism of **24.** The free-energy barrier ΔG^*_{273} was found to be 50 kJ mol^{-1} in CD_2Cl_2 solution from the line width temperature dependence of the NH signal in ^{1}H NMR. A value of 46 kJ mol^{-1} for the free-energy barrier to proton migration was obtained in more accurate ^{15}N NMR experiments (82JOC5132). A mechanism based on proton interaction with the unpaired electron of hypothetical short-lived radicals of polycrystalline pyrazole, imidazole, and benzotriazole was considered as a possible factor in the proton exchange reaction (91JPO271).

5. *1,2,4-Triazoles*

Annular prototropic tautomerism of 1,2,4-triazoles (*s*-triazoles) involves an equilibrium between three possible forms (**26a**–**26c**) (Scheme 13).

For the unsubstituted 1,2,4-triazole ($R^1 = R^2 = H$) the degenerate iso-



SCHEME 13

mers **26a** and **26b** are highly preferable energetically compared to **26c.** The intrinsic energy difference between the two tautomeric forms is 21 kJ mol^{-1} according to *ab initio* DZ calculations [81ZN(A)1246]. The theoretical prediction is in accord with the results of photoelectron [81ZN(A)1246], IR (96LA1041), and microwave [71JCS(CC)873] spectral studies of 1,2,4-triazole as well as with those of an X-ray crystal study [69AX(B)135; 97ZK(212)213]. With the growing interest in 1,2,4-triazoles as compounds with high and specific biological activity, a wealth of crystallographic studies on a wide range of derivatives have been reported, see [92AX(C)342; 94AJC309; 96CHEC-II(4)127] and references therein. Regardless of the substituents R^1 and R^2, all N-unsubstituted 1,2,4-triazoles preserve the 1*H* or 2*H* structures **26a** or **26b.** In a 1:1 adduct with 1,1-di(2,4-dimethylphenyl)but-2-yne-1-ol, 1,2,4-triazole also exists as the 1*H* tautomer (87CL2317). Gas-phase basicities and thermodynamic properties of 3-trifluoromethyl-1,2,4-triazole and 3,5-bis(trifluoromethyl)-1,2,4-triazole have recently been studied (94JOC1039; 95OPP33). Combined with the ^{19}F and ^{13}C NMR spectra and high level (MP2/6-31G*) *ab initio* calculations, significant energy preferences for the 1*H* tautomers **26a** ($R^1 = CF_3$, $R^2 =$ H) and **26a** ($R^1 = R^2 = CF_3$) were confirmed unequivocally. In the case of 3-amino-1,2,4-triazole **26** ($R^1 = NH_2$, $R^2 =$ H) (78K849) and 5-amino-3-trifluoromethyl-1,2,4-triazole [98AX(C)442], the 2*H* tautomers **26b** exist in the solid state according to an X-ray study. The same tautomeric form type is also characteristic for 3,5-diamino-1,2,4-triazole **26** ($R^1 = R^2 = NH_2$), which has in crystal the structure **26a** (79KGS1422). A study of 3-amino-1,2,4-triazole in aqueous solution using ^{15}N NMR spectroscopy also concludes that the 2*H* tautomer dominates with the **26b:26a** ($R^1 = NH_2$, $R^2 =$ H) ratio being approximately 2:1, whereas the 4*H* tautomer **26c** is not present to any measurable extent. These findings are in accord with recent high-level *ab initio* calculations [92JCS(P2)1681] of the relative energies of the three tautomers in the gas phase. At the CCSD/6-31G**//G-31G** and MP2/6-31TG** levels of theory, the 1*H* and 2*H* tautomers are essentially isoenergetic in the gas phase, with the 4*H* tautomer having 29 kJ mol^{-1} higher energy. Semiempirical methods fail to reproduce the correct order of stabilities of the three tautomers. However, IR and X-ray studies (81MI511) of crystalline 3-substituted ($R^1 =$ Cl, Br, I) triazoles indicate structure **26c** for the chloro and bromo derivatives. For the iodine derivative, both tautomeric forms were found to coexist in the crystal.

Semiempirical MNDO (85JOC4894, 95ZOR1422) and AM1, PM3 (95ZOR1422), and *ab initio* (95JPC12790) calculations conclude that the unfavorable tautomer **26c** ($R^1 = R^2 =$ H) has a substantially higher dipole moment than **26a:** 5.86 D and 3.01 D, respectively (95JPC12790). This factor provides for better solvation of **26c** in dipolar solvents and leads to a

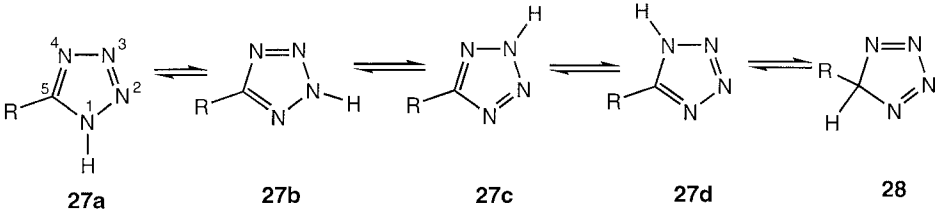
partial shift of the tautomeric equilibrium toward it. Thus, about 5% of **26c** were observed in the ^{15}N NMR spectrum of 1,2,4-triazole in DMSO solution (82JOC5132, 97MRC35).

An estimate of the energy barrier to the degenerate tautomerization **26a** ⇌ **26b** of 1,2,4-triazole has been obtained from temperature-variable ^1H NMR spectra [77DOK1380, 84JCS(P2)1025]. The Arrhenius plots lnk^{-1}/T of the reaction in HMPT and dimethoxyethane solutions are not linear but can be represented by two straight lines intersecting at 263–293 K. At higher temperatures, the values of activation energy were found to be substantially lower than those calculated for the lower temperature region. Thus, in HMPT solution E_a = 75.3 kJ mol^{-1} and 28.5 kJ mol^{-1} for the intervals of temperature between 253–273 K and 273–333 K, respectively. The free-energy barriers ΔG^*_{273} were found to be equal to 61.5 kJ mol^{-1} (HMPT), 64.9 kJ mol^{-1} (DME) (77DOK1380), and 57.3 kJ mol^{-1} (CD_2Cl_2) [84JCS(P2)1025].

6. *Tetrazole and Its Derivatives*

Four pairwise degenerate tautomeric forms referred to as the 1*H* (**27a** and **27d**) and 2*H* (**27b** and **27c**) tautomers are needed to describe the annular prototropic tautomerism of unsubstituted tetrazole **27** (R = H) (Scheme 14).

The position of this equilibrium is very sensitive to substituents in the ring and also to the medium surrounding the rearranged tetrazole molecules. For unsubstituted tetrazole **27** (R = H) (74CSC321) and its 5-trichloromethyl derivative **27** (R = CCl_3) [87ZN(B)55], X-ray crystallography showed that only the 1*H* tautomer exists in the solid state. Tetrazole molecules form long intermolecular chain structures with (1)NH···N(4) hydrogen bridges between adjacent rings, thus giving planar sheets separated by 3.35Å [97AX(C)590]. The 1*H* tautomer **27a** ⇌ **27d** of tetrazole was found also to be the major form in the solid state by ^{13}C CPMAS NMR study (83H1713). A rare example of desmotropic behavior related to sta-



SCHEME 14

bility of two tautomeric forms of the tetrazole moiety of irbesartan, a novel antihypertensive agent (angiotensin II antagonist), has been recently reported [98JCS(P2)475, 98JCS(P2)2671].

Much effort has been devoted to the study of annular tautomerism of tetrazoles in the gas phase. Photoelectron spectroscopic evidence allowed the firm conclusion that the 2*H* tautomer **27b/27c** is preferred for unsubstituted tetrazole [81ZN(A)1246]. However, microwave (74JSP423), IR (96LA1041), UV photoelectron (87CP249), and mass spectrometry studies of the prototropic equilibria in tetrazole and 5-substituted (R = CH_3, CD_3, CF_3, NH_2) tetrazoles [69OMS433; 70JHC1223; 83JCS(P2)379] indicated the presence of both the 1*H* and 2*H* tautomers in the gas phase, the latter usually being preferred. Mass spectrometric results do not necessarily reflect tautomeric equilibria of neutral species **27** and may be related to their ions; therefore, deductions from this method are to be treated with caution. For this reason, much theoretical work has been done to check on these results and gain deeper insight into the problem of annular tautomerism of tetrazoles in the gas phase. Most of this work has been thoroughly reviewed previously [71JCP249; 76AHC(S1), p. 287; 82JST283; 84CHEC-I(5)791, 84CS (24)84; 85JPC460; 94UK847; 95ZOR1422; 96CHEC-II(4)621]. The highest level *ab initio* calculations relevant to the study of the tautomeric equilibrium of tetrazole include the use of 6-311+G(2d,2p) basis set with electron correlation incorporated at the QCISD(T) level with appropriate ZPVE corrections (93JA2465) and the MP4/6-31G//MP2/6-31G* approach [95JST(T)9]. At these levels, 2*H* tautomer **27b** (R = H) of tetrazole was found to be 7.7 and 11.1 kJ mol^{-1} intrinsically more stable than its 1*H* isomer **27a.** An important conclusion stemming from the calculations [93JA2465; 95JST(T)9] is reversal of the predicted stability of **27b** relative to **27a** from low levels of theory, e.g., RHF/3-21G. Thus, conclusions from *ab initio* calculations at levels lower than RHF/6-31G* may be misleading.

The theoretical study (93JA2465) dealt also with examination of the solvent effect on the tautomerism of tetrazole in the liquid phase by the self-consistent reaction field (SCRF) method. The energy difference between the tautomers in solution was estimated from the gas-phase ΔE values at the QCISD(T) level together with solvation energies calculated at the MP2 level. Entropy changes were calculated from the theoretical vibration frequencies. The calculated free energies, ΔG^0, of tautomerization for 1*H*-tetrazole were -7 (gas phase), 1, and 12 kJ mol^{-1} in solutions of solvents with dielectric constants $\varepsilon = 2$ and 40 respectively. These results suggest that the tautomeric equilibrium of tetrazole is strongly dependent on solvent polarity. In polar media, tetrazole was predicted to exist predominantly as the 1*H* tautomer, in contrast to the preference of the 2*H* tautomer in the gas phase.

The computational results (93JA2465) are consistent with the experimental findings of ^{15}N NMR spectroscopic studies (82JOC5132; 97MRC35), which showed the presence of only the 1*H* tautomer of tetrazole in DMSO-d_6 ($\varepsilon = 49$) solution. The content of 1*H* tautomer **27a** in dioxane ($\varepsilon = 22$) at 30°C was estimated as 78% (82JST283) and 85% (75BSF1675) from its dipole moment 4.88 D and those of 1,5- and 2,5-dimethyltetrazoles as models for the 1*H* and 2*H* tautomers respectively.

The influence of substituents R in the five-membered ring of **27** on the position of the tautomeric equilibria is illustrated by the data collected in Table IV.

In general, electron-releasing substituents R (NH_2, SCH_3) shift the equilibrium **27a** ⇌ **27b** toward the 1*H* tautomers **27a.** With respect to the substituents in the 5-phenyl ring, the most conspicuous effect is that of *ortho* groups, which cause out-of-plane rotation of the aryl ring and drive the equilibrium toward the 1*H* tautomers [81JCS(P1)390; 84CHEC-I(5)791].

The energy barrier to the intramolecular 1,2-hydrogen shift from 1*H*-tetrazole **27a** to 2*H*-tetrazole **27b** (R = H) was calculated at the QCISD(T)/6-311+G(2d,2p) + ZPVE level as 207 kJ mol^{-1} [93JA2465; 98JCS(P2)2671]. The presence of a base (e.g., NH_3) facilitates 1,2-H shift, lowering the proton transfer barrier to 119 kJ mol^{-1} [98JCS(P2)2671]. A very high energy barrier (232 kJ mol^{-1}) must be overcome for the rearrangement of 1*H*-tetrazole to its unknown 5*H* tautomer **28.**

TABLE IV

TAUTOMERIC EQUILIBRIUM CONSTANTS K_T = [1*H*]/[2*H*] OF SUBSTITUTED TETRAZOLES **27** IN DMSO ESTIMATED FROM ^{13}C NMR STUDIES

R	K_T	Reference
5-NH_2	13.3[a]	84CHEC-I(5)791
5-CH_3	1.2[a]	84CHEC-I(5)791
5-Cl	0.9[a]	84CHEC-I(5)791
5-SCH_3	5.7[b]	85BAP375
5-Ph	6.1	84CHEC-I(5)791
5-$C_6H_4CH_3$-4′	7.3[c]	84CHEC-I(5)791
5-$C_6H_4CH_3$-2′	6.1	81JCS(P1)390
5-$C_6H_4NO_2$-4′	2.1	84CHEC-I(5)791
5-$C_6H_4NO_2$-2′	3.5	84CHEC-I(5)791
5-C_6H_4Cl-4′	2.0	84CHEC-I(5)791
5-C_6H_4Cl-2′	10.1	81JCS(P1)390
5-$C_6H_3Cl_2$-2′,6′	10.1	81JCS(P1)390

[a] Solvent DMSO–water 4:1.

[b] From ^{15}N NMR spectra.

[c] In dioxane solution at 30°C, content of 1*H* tautomer is 60 ± 10% according to dipole moment measurements (80JHC1373).

Due to the lack of aromaticity, **28** is predicted to be 82 kJ mol^{-1} (93JA2465) or 120 kJ mol^{-1} [95JST(T)9] less stable than **27a;** the energy barrier for reverse rearrangement of **28** to **27a** is also high, about 150 kJ mol^{-1}. Such an energy barrier would ensure kinetic stability of **28** and make it an experimentally accessible species. High values of the energy barriers for intramolecular hydrogen shifts in tetrazole suggest that annular prototropic tautomerism is governed by the mechanisms similar to those considered in Section I,B,1 which involve dimerization or solvent-assisted double proton transfers.

C. Elementotropic Annular Tautomerism

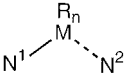
Until the 1960s, the concept of tautomerism was usually identified with prototropy. The discoveries of fast and reversible circumambulation of organometallic and organoelement groups in the cyclopentadiene ring [56JINC32; 75JOM(100)29] and the first tautomeric systems in which migration of organometallic groups occurs between two heteroatoms [60DOK331; 75JOM(100)161] initiated rapid progress in studies of the migrating abilities of such groups in various organic systems including azoles. At present, data are available on elementotropic tautomerism due to displacements of main-group 12–15 element-centered groups and organometallic groups derived from a number of transition metals between nitrogen centers in pyrazole, imidazole, 1,2,3-triazole, their benzoannulated derivatives, and 1,2,4-triazole. These data have been extensively reviewed [73MI71, 73UK177; 81UK1304; 84CHEC-I(5)167, p. 225; 84ZSK163] and here we discuss mostly the more recent results with emphasis on general trends related to migratory aptitudes of various groups and mechanisms of the tautomeric rearrangements.

1. *Mechanisms of Elementotropic Tautomerism*

Migration of an organoelement group, attached to a pyrrole-type nitrogen, to a pyridine-type nitrogen of the same (intramolecular rearrangement) or another (intermolecular rearrangement) molecule involves a nucleophilic substitution at the migration center.

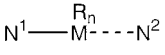
Qualitative models of reactivity and quantum mechanical calculations of reaction paths both indicate an angular approach of the attacking nucleophile to the first-row sp^2-hybridized electrophilic centers M at intermediate and reactive distances, **29.** The geometry of **29** is also characteristic for the case of nucleophilic addition to electron-deficient centers of main-group 12 and 13 elements. By contrast, a linear arrangement **30** of making and breaking bonds is required for sp^3-hybridized first-row centers (C, N, O)

and for any second-row- and lower element-centered migrants (88MI1; 89PAC661). Steric demands of the transition metal centers are less stringent because of their diffuse orbital ensuring nonzero overlap even at less favorable orientations of the interaction centers.



$MR_n = BR^1R^2$, GaR^1R^2, C(O)R, Aryl, NO, NO_2

29



$MR_n = CR^1R^2R^3$, PR_2^+, PR_3, $P(O)R^1R^2$, SR, S(O)R, SO_2R

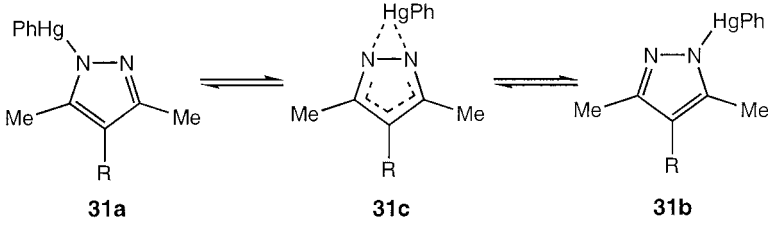
30

Fitting a rearranged system to the steric requirements shown above within a molecule is needed for an intramolecular mechanism. Even when the appropriate arrangement cannot be achieved within a single molecule, the required configuration, **29** or **30,** can possibly be realized in a dimer or higher associate. For metal-centered migrants, an alternative intermolecular mechanism of the dissociative S_N1 type is also possible.

2. *Mercurotropy*

Degenerate rearrangements of the 1-phenylmercury-3,5-dimethylpyrazoles **31** are apparently the first example of metallotropy in the series of azoles (71DOK110) (Scheme 15).

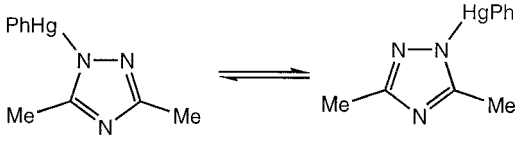
At room temperature and down to −90°C ^{1}H-NMR resonances of methyl groups appear as a common singlet peak (υ = 60 MHz, solvent $CH_2Cl_2/CHCl_3$), which splits into two broadened signals near −110°C. Although no quantitative estimates of the activation parameters were presented, the spectral behavior clearly indicates fast migration of a phenylmercury group between the two ring nitrogens at a rate comparable to that



31a **31c** **31b**

R = Cl, Br, NO_2

SCHEME 15



32a **32b**

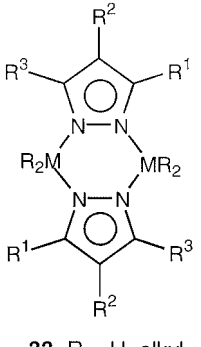
SCHEME 16

of proton migration in pyrazoles with MR_n = H. The spectral patterns observed were not affected by concentration of the solutions and by addition of appreciable amounts of pyridine or CD_3NO_2, which might well solvate the cation $PhHg^+$ in the event that the rearrangement followed the dissociation–recombination pathway. It was concluded that the tautomeric rearrangement **31a** ⇌ **31b** is intramolecular and involves the transition state or intermediate structure **31c.**

The same type of mechanism was suggested for the tautomeric 1,2 shifts of a phenylmercury group in 1,2,4-triazole **32** (Scheme 16). It was reported (84MI204) that the frequencies of a phenylmercury group migration **32a** ⇌ **32b** are even higher than those of proton migration in the corresponding NH compound.

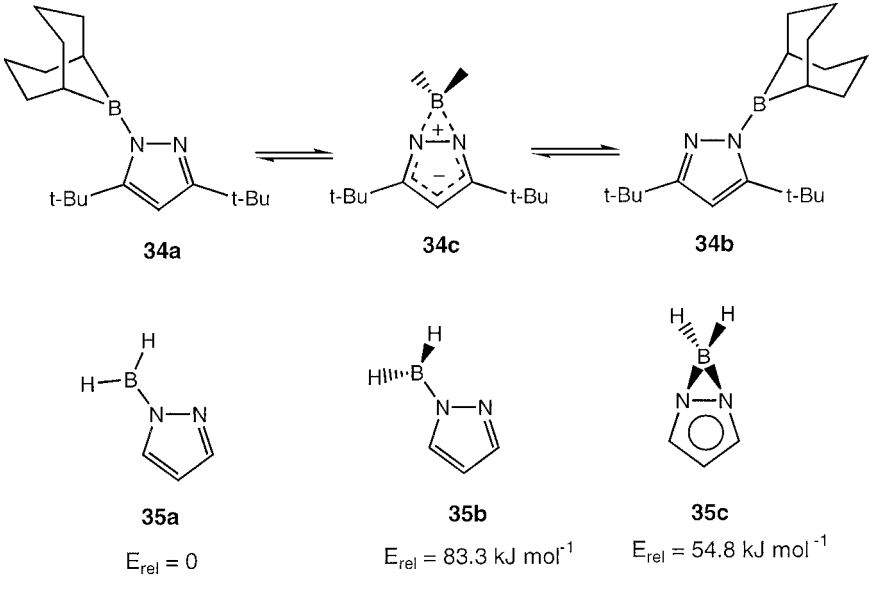
3. *Tautomeric Migration of Main-Group-13 Element-Centered Groups*

Substitution of the N^1H hydrogen atom of pyrazole by such groups as BR_2, AlR_2, GaR_2, and TeR_2 gives organometallic derivatives which possess in solution and in the solid state the dimeric structure **33,** similar to the hydrogen bonded dimers, with the difference being that all the M-N bonds in **33** are equidistant [66JA1842; 67JA3165; 71ACR17; 72CRV497, 72ZOB920; 73JCS(D)2252; 74JCS(D)503; 87MI245; 98AHC(72)1].



33, R = H, alkyl

The first monomeric diorgano(pyrazolyl)borane **34** showed very high fluxionality (Scheme 17). Migration of the B(III)-center could be frozen on the NMR time scale only at −100°C [90AG(E)302]. The intermediacy of the nonclassical symmetric structure **34c** has been confirmed by *ab initio* MP2(full)/6-31G* calculations of model pyrazolylboranes **35,** which identified **35c** as a local minimum on the corresponding potential energy surface [90AG(E)304].



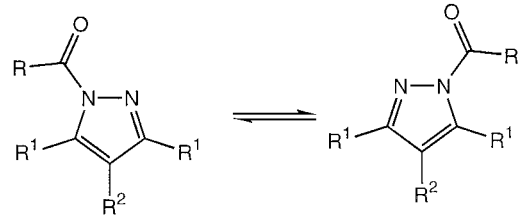
SCHEME 17

Very fast N,N-migrations of a dimethylgallium group were reported to occur in solutions of *N*-dimethylgallium pyrazole [81JOM(215)157].

4. *Carbonotropy*

In N-substituted pyrazole and other azoles, stereoelectronic conditions for the intramolecular 1,2 shifts of both $C_{sp}{}^2$- and $C_{sp}{}^3$-centered groups are unfavorable in **29** and **30.** Therefore, all currently known examples of N,N-migration of such groups in this series of compounds are intermolecular.

Rapid exchange of positions was observed for acyl and amidoyl groups in the ^{1}H NMR spectra of compounds **36** in 1-chloronaphthalene solution at high temperatures (170–215°C) (Scheme 18). [72JCS(CC)709]. Crossover experiments clearly indicated the intermolecular exchange. The value of the free-energy barrier was determined as $\Delta G^* = 100$ kJ mol^{-1} at the coales-



36a **36b**

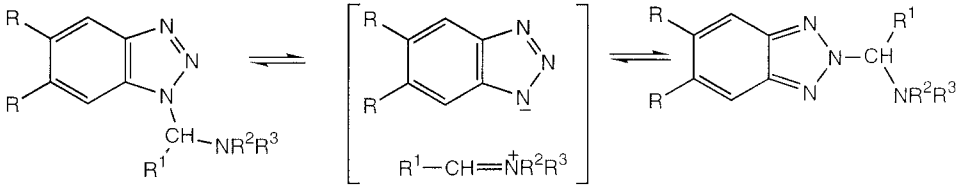
R = *t*-Bu, NHPh, NHC_6H_4Me-*p*, $C_6H_4NO_2$-*p*, $C_6H_3(NO_2)_2$-2,4;
R^1 = Me, *t*-Bu; R^2 = H, Me

SCHEME 18

cence temperature (195°C) of the methyl groups in **36** (R = NHPh, R^1 = Me, R^2 = H).

No N,N-migration of an acyl group (73ZOR1319) or a 2,4,6-trinitrophenyl (picryl) group (76ZOR1271) was observed in solutions of *N*-acyl- or *N*-picryl-3,5-dimethylpyrazole at high temperatures, although migrations of a picryl group in derivatives of tropolone, aminotropone imine, and hydroxyphenalenone, all with the favorable steric arrangement **29,** proceed at rates of the same order as those of the corresponding proton migrations (88MI1). Recent results show that 1-acyl-1*H*-pyrazol-5(2*H*)-ones prepared *in situ* can transform into 1-acyl-3-hydroxy-1*H*-pyrazoles, that formally involves N,N-migration of *N*-acyl group. The transformation is assisted by the nucleophilic oxygen of 1,4-dioxane used as a solvent or by intermolecular migration of the acyl group between two molecules of the starting pyrazolone derivative [98JCS(P1)2813].

Particular attention has been given to the study of thermal rearrangements of N-substituted benzotriazoles. *N*-(*N*′,*N*′-Dialkylaminomethyl) benzotriazoles exist in the solid state solely as the isomers **37a,** but in the liquid, solution, melt, and argon matrix phases they form equilibrium mixtures of the tautomers **37a** and **37b** (Scheme 19) [76JCS(P2)741;



37a **37c** **37b**

SCHEME 19

TABLE V

EQUILIBRIUM CONSTANTS K_T = **37a/37b** AS DETERMINED USING ^{1}H NMR SPECTRAL DATA (ROOM TEMPERATURE) [87JCS(P1)2673]

Compound				
R	R^1	$R^2 = R^3$	Solvent	K_T
H	H	Me	$CDCl_3$	4.3
H	H	$-(CH_2)_2-$	$CDCl_3$	5.5
			DMSO	>9
H	H	Et	$CDCl_3$	2.2
				>9
Me	H	$-(CH_2)_2-$	$CDCl_3$	5.1
Me	H	Et		2.5

87JCS(P1)2673; 89H1121]. As proven by crossover experiments, interconversion of the tautomers occurs intermolecularly, an ion pair **37c** being the intermediate in the dissociation–recombination mechanism of the rearrangement.

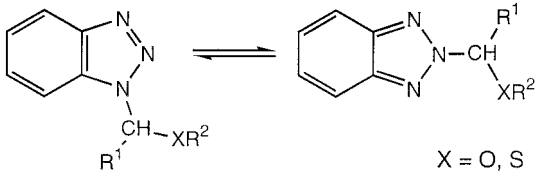
As seen from Table V, the N1 tautomer is the major form in the equilibrium.

Ab initio 6-31G*//3-21G calculations of a model *N*-(dimethylaminoaminomethyl)benzotriazole **37** (R = R^1 = H, R^2 = R^3 = Me) correctly reproduce the experimental findings indicating a slight preference for the N1 tautomer **37a,** but semiempirical methods fail (90JOC5683).

Similar isomerization reactions were observed in $CDCl_3$ solutions of *N*-(α-aminomethyl)-1,2,4-triazoles and -tetrazoles (90T633). As for the analogous benzotriazoles, these reactions are intermolecular and slow at 20°C in the NMR time scale.

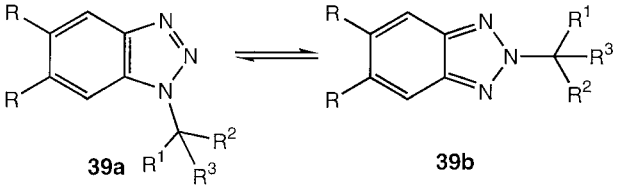
In contrast to the compounds **37,** which undergo rapid equilibration in solution, the isomers **38a** and **38b** of their sulfur and oxygen analogs **38** (Scheme 20) interconvert less rapidly and can be separated (89JOC6022; 91HCA1924), as can some *N,N*-bis(benzotriazolylmethyl)arylamines **37** (R^2 = aryl, R^3 = benzotriazolylmethyl) (90CJC446).

Some *N*-arylmethylbenzotriazoles **39** show faster equilibration (Scheme



38a **38b**

SCHEME 20



SCHEME 21

21). Compounds **39** were prepared by the alkylation of benzotriazoles with the corresponding diarylmethyl chloride and the mixtures of isomers were subsequently chromatographically separated. Isomerizations were carried out by heating pure dry samples of either **39a** or **39b** at 175–250°C and the ratios were estimated from the ^{1}H NMR signal intensities. The attainment of thermodynamic equilibrium was confirmed by the almost-identical ratios of **39a** and **39b** obtained by heating either of the isomers [90JCS(P2)2059]. Table VI summarizes the results of isomerization of compounds **39.**

From the data presented in Table VI, the substituents R^1 and R^2 strongly affect the rates of the isomerization; *N*-benzyl derivative **39** ($R = R^3 = H, R^1 = R^2 = Ph$) did not undergo isomerization at a detectable rate at 250°C. On the other hand, the compounds **39** ($R = R^3 = H, R^1 = R^2 = C_6H_4NMe_2$-*p*) and **39** ($R = R^3 = H, R^1 = R^2 = C_6H_4OMe$-*p*) reached equilibrium in less than 5 min at 215°C.

As for compounds **37,** the rearrangements of **39** are considered to occur by a mechanism involving heterolytic N-C bond cleavage followed by intermolecular recombination of the carbenium cation and benzotriazolyl anion so formed.

TABLE VI

THERMAL ISOMERIZATION OF COMPOUNDS **39**[a]

Compound **39**			Initial isomer	Time of heating, h	*T* (°C)	Equilibrium ratio, N1 : N2
R	$R^1 = R^2$	R^3				
H	Ph	H	N1	8	250	72 : 28
			N2	5	215	84 : 16[b]
H	$C_6H_4NMe_2$-*p*	H	N1	0.08	175	74 : 26
			N2	0.08	215	75 : 25
H	C_6H_4OMe-*p*	H	N1	0.08	215	75 : 25
			N2	3	215	72 : 28
H	C_6H_4Cl-*p*	H	N1	0.5	215	58 : 42
			N2	3	215	60 : 40
Me	C_6H_4OMe-*p*	H	N1	0.5	250	69 : 31
			N2	0.5	250	68 : 32
Me	Ph	Ph	N1	0.5	250	55 : 45
			N2	0.5	250	56 : 44

[a] 90JCS(P2)2059.

[b] Isomerization takes place only in the presence of $ZnCl_2$.

5. *Si-, Ge-, and Sn-Centered Migrants*

The trigonal–bipyramidal structures with a central carbon atom involved in the S_N2 reaction for the silicon, germanium, and tin analogs are not transition states but intermediates. Although such intermediates are the most stable with the electronegative group N^1 and N^2 (**30**) at the diaxial position, the topomers containing these groups in the axial–equatorial arrangement are rather close energetically. Moreover, pentacoordinated C_s-structures with the angular arrangements of the N^1 and N^2 groups, **29,** also do not differ much in energy from the lowest energy configuration [80JOM(198)231; 85JA6352; 88MI1]. Therefore, the possibility exists for intramolecular N,N- shifts of silyl and congeneric migrants in pyrazole and other azoles with vicinal nitrogen centers. Such a suggestion was made in 1966 (66CB2512) and was soon supported by data from the ^{1}H NMR study of the degenerate silylotropic rearrangements of 1-(trimethylsilyl)pyrazoles **40** (M = Si, R = Me, R^1 = H, Me, CF_3, R^2 = H, Me) [71JOM(27)185].

No significant influence of concentration of the solution and nature of solvent on the rate of rearrangement was found in this and subsequent studies (81UK1304; 95MI279), which is in accordance with an essentially intramolecular character of the exchange reaction. Table VII includes

TABLE VII

ENERGY BARRIERS TO THE TAUTOMERIC REARRANGEMENTS **40a** ⇌ **40b** AS DETERMINED BY ^{1}H AND ^{13}C NMR SPECTROSCOPY

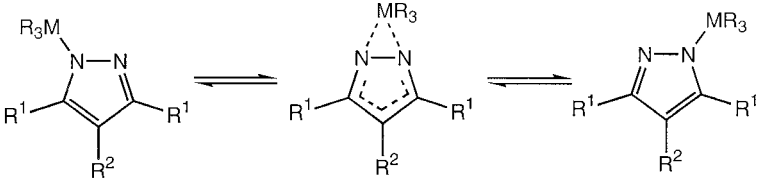
Migrating group MR_3	R^1	R^2	Solvent	E_a, kJ mol^{-1}	Reference
$SiMe_3$	H	H	Ph_2O	~134	71JOM(27)185
	H	Cl	$PhNO_2$-d_5	100[a]	95MI279
	H	Br	$PhNO_2$-d_5	99.5[a]	95MI279
	H	NO_2	$PhNO_2$-d_5	>100[a]	95MI279
	Me	H	Ph_2O	117	71JOM(27)185
	Me	H	Liquid	96[b]	74JOM(70)347
	Me	Me	Ph_2O	100	71JOM(27)185
	CF_3	H	Ph_2O	—[c]	71JOM(27)185
$SiEt_3$	Me	H	Liquid	96	74JOM(70)347
$Si(OEt)_3$	Me	H	Liquid	106	74JOM(70)347
$GeMe_3$	H	H	Liquid	92	72MI197
	Me	H	Liquid	84[b]	74JOM(70)347
$SnBu_3$	H	H		—[d]	77JOM(132)69

[a] Free energy barriers, $\Delta G^{\ddagger\ddagger}$ calculated at coalescence temperature of signals H-3, H-5, or Me-3, Me-5.

[b] $\Delta G^{\ddagger\ddagger}$ at 300 K.

[c] T_c for coalescence of ^{1}H NMR resonances of methyl groups is 170°C.

[d] $T_c \ll -80$°C.



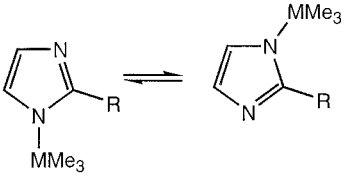
SCHEME 22

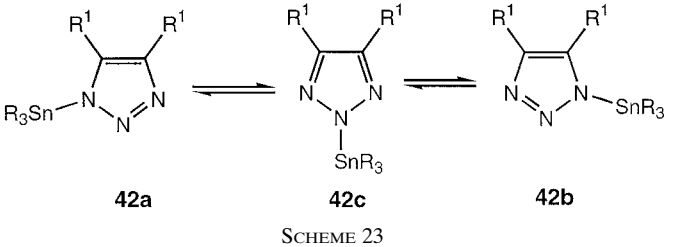
kinetical data on type **40a** ⇌ **40b** degenerate annular tautomerism (Scheme 22).

From the data collected in Table VII, it follows that the migratory aptitude of the Si-, Ge-, and Sn-centered groups in the rearrangement **40a** ⇌ **40b** increases from SiR_3 to SnR_3 groups.

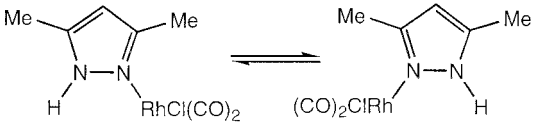
Derivatives of imidazole **41** also exhibit fast degenerate rearrangement, which, unlike those of pyrazole derivatives, are exclusively intermolecular and also very sensitive to the influence of traces of water (Scheme 23) [74JOM(70)347; 76IC3054; 77JOM(132)69].

In ^{13}C NMR spectra of trialkyltin derivatives of 1,2,3-triazoles, C(4) and C(5) atoms show one common signal at the lowest attained temperature of solution, −50°C [77JOM(132)69]. This observation was explained by the symmetric structure **42c** of the compounds (R^1 = COOMe) [77JOM(127)273]. However, rapid annular tautomerism explains this observation equally well and cannot be ruled out.





SCHEME 23



43a **43b**

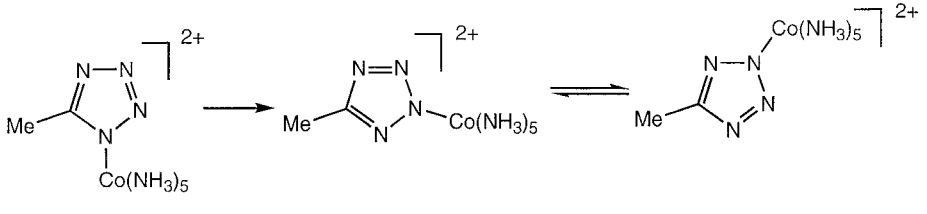
SCHEME 24

6. *Transition Metal-Centered Migrants*

Tautomeric rearrangements of transition-metal complexes with azole ligands are relatively scarce. The fluxional behavior of the rhodium complex **43** with a neutral 3,5-dimethylpyrazole was explained as the result of rapid processes of metallotropy and prototropy occurring simultaneously (Scheme 24) [74JOM(C)51].

In a similar complex containing a Ru-centered group, Ru(CO)(*i*-PrTTP)[2] instead of rhodium, the activation energy for the rearrangement was found to be 71 kJ mol^{-1}. The exchange reaction was suggested to comprise intermolecular ligand dissociation and reentry [72JOM(39)179].

However, results of the ^{15}N NMR studies of rearrangements of (5-methyltetrazolato)pentaamminecobalt(III) **44** (93IC2394; 94IC1921) and a similar (4-methylimidazolato)complex (94IC1921) contrast with this conclusion (Scheme 25). Using regiospecifically ^{15}N-labeled complexes, irreversible linkage isomerization **44a** → **44b** and degenerate tautomeric rearrangement **44b** ⇌ **44c** have both been shown to be intramolecular in DMSO and water as solvents. η^2-Structures similar to **31c** and **40c** were suggested as intermediates. Both rearrangements are subject to acid catalysis, the site of protonation in **44a** and **44b** being the N(4) atom. The faster rearrangements (10- to 100-fold acceleration) of the complexes with neutral ligands thus formed are also intramolecular (94IC1921).



44a **44b** **44c**

SCHEME 25

[2] *i*-PrTPP is the tetrakis(*p*-isopropylphenyl)porphinate dianion.

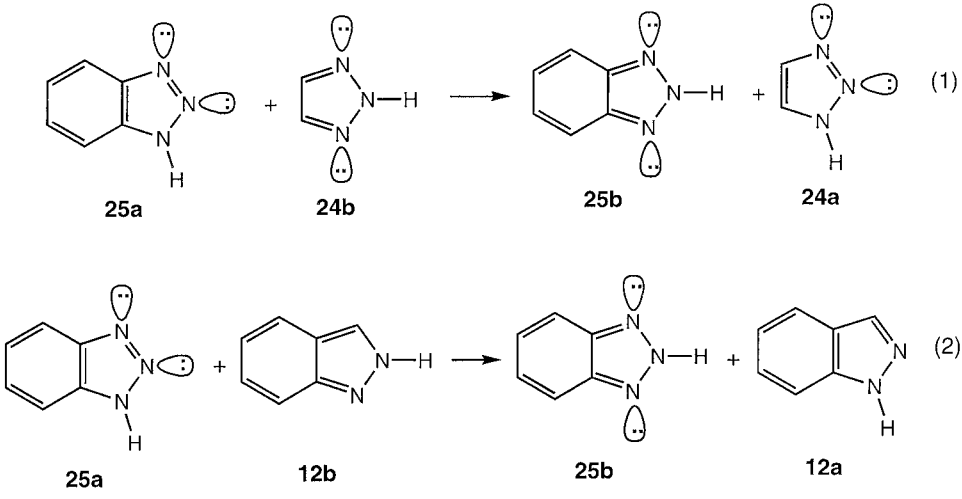
D. General Conclusions on the Factors Affecting Annular Tautomerism

Despite the special features characteristic of annular tautomerism in each individual azole system, some generalization regarding the thermodynamics and kinetics of these tautomeric equilibria and their dependence on structure and media can be proposed.

1. *Intrinsic Stability*

For all the heterocycles considered in this chapter, nonaromatic isomers formed through the migration of a hydrogen atom to a ring–carbon atom, such as **2c–2e** and **28,** are highly energetically unfavorable and, therefore, unobservable in the tautomeric equilibria. Aromaticity should be regarded as an important factor governing intrinsic stability of annular tautomers. The clearest evidence of the role of this factor is given by indazole, where the energy preference of tautomer **12a** over **12b** is fully determined by the higher degree of aromaticity inherent in **12a** [96JCS(P2)57]. The concept of aromaticity may in principle be invoked in the form of its structural or magnetic criteria [91H127; 93AHC(56)303] for the prediction of preferential tautomers in the triazole and tetrazole systems. However, due to the small energy differences between annular tautomers such an approach has little value. Better rationalization is achieved through consideration, together with aromatic stabilization, of a destabilizing factor identified [86JA3237; 90JST(T)367] as lone-pair repulsion between adjacent sp^2 nitrogen centers. Whereas in the case of 1,2,3-triazole **24** both these factors favor the 2*H* tautomer **24b,** in benzotriazole they act oppositely: the 1*H* tautomer **25a** is more aromatic than the 2*H* tautomer **25b,** but suffers from greater repulsion of closer-spaced electron lone pairs. A correct balance of the two factors is achieved only at sufficiently high level of *ab initio* calculations with electron correlation taken into account (94JOC2799). By using an approach based on isodesmic reactions, one can estimate the contributions of each of the two factors on the relative stability of the equilibrating tautomers of benzotriazole.

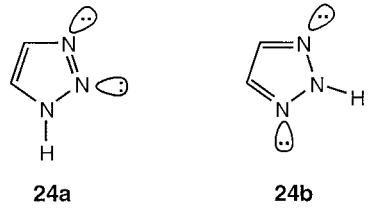
Assuming that aromatic stabilization of **24a** and **24b** is of the same magnitude, and this is also true for the lone-pair repulsion in the pairs **24a/25a** and **24b/25b,** the energy, ΔE, of the isodesmic reaction (1) corresponds to the contribution from greater aromatic stabilization of **25a** with respect to **25b** (Scheme 26). At the MP2/6-31G** approximation, $\Delta E = 10.5$ kJ mol^{-1} (94JOC2799). Similar arguments applied to the isodesmic reaction (2) allow estimation of the energy contribution due to the repulsion of adjacent lone pairs in **25a.** In MP2/6-31G** approximation, $\Delta E = -25.9$ kJ mol^{-1}



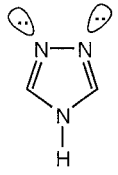
SCHEME 26

[96JCS(P2)57]. It follows, therefore, that the destabilizing lone-pair repulsion effect appeared in the 1*H* tautomer **25a** overcomes positive contribution of its greater aromatic stabilization relative to **25b** and serves as a major factor defining the relative stability of the tautomers.

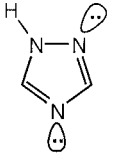
Some ambiguity exists about the origin of the effect as defined in classical terms and evaluated in the framework of a quantum mechanical approach. However, even without attributing to the effect a specific term in the total energy partitioning scheme, the model based on lone-pair repulsion leads to correct predictions of the intrinsically most stable tautomers for all the azoles. The pairs of annular tautomers of triazoles and tetrazole are shown below, those most stable with none or less adjacent electron lone pairs are pictured next to the energetically unfavorable forms. The energy differences from currently available highest level *ab initio* calculations are to be compared with the 25.9 kJ mol^{-1} increment [96JCS(P2)57].



ΔE(MP2+6-31G**//3-21G) = -14.8 kJ mol^{-1} (91JPC3123)

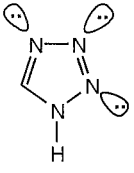


26b

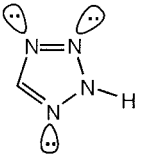


26a

ΔE(RHF/DZ) = -21 kJ mol^{-1} [81ZN(A)1246]



27a



27b

ΔE(MP4/6-31G*//MP2/6-31G*) = -11.1 kJ mol^{-1} [95JST(T)9]

It should be emphasized that the correct description of the peculiar effect brought about by the presence of two or more sp^2-nitrogen centers within a molecule can be reproduced reliably only by high level *ab initio* calculations accounting for electron correlation. This conclusion is well justified by the examples of benzotriazole, 3-amino-1,2,4-triazole, and tetrazole, as described in Sections II,B,3; II,B,4; and II,B,5, respectively.

2. *Effects of Medium and State of Aggregation*

As expected, tautomers possessing higher dipole moments are better solvated in polar solvents. The energy of solvation of an azole in solvents such as water, methanol, or DMSO may amount to 90 kJ mol^{-1} (89JA7348), and the differential energy of solvation of tautomers can easily be of the same order of magnitude as their relative energy. In certain cases a gain in the solvation energy of an unfavorable tautomer exceeds its lower intrinsic stability and it becomes an observable or even a predominant species in solution. Examples of this type are numerous: 1,2,3-triazole, 1,2,4-triazole, 3-amino-1,2,4-triazole, and tetrazole. Attempts of limited success at quantitative assessments of contributions of the differential solvation of tautomers to annular tautomerism have been based on the two most developed theoretical models: the self-consistent reaction field (SCRF) method (91JA4776; 93JA2465) and the polarizable continuum (PCM) method (81CP117). While giving qualitatively correct predictions of the differential solvation effects, neither model was able to reproduce quantitatively the

relative energies of the hydrated tautomers for the case of 3-amino-1,2,4-triazole [92JCS(P2)1681]. The most probable reason for this is the inability of these theories to account for the specific effects of formation of hydrogen bonds between molecules of solute and solvent. These effects play apparently a crucial role in formation of associates of azoles and their H-complexes with proton-donor and proton-acceptor solvents. As shown by X-ray studies of pyrazoles, it is precisely the networks of hydrogen bonds formed by azole molecules in crystal which determine stability of this or that tautomeric form and even the coexistence of both in the solid state. In general, the tautomer found in crystal is also the most stable tautomeric form observable in solution.

The network of hydrogen bonds in dimers and oligomers is also a major factor determining the mechanism and kinetics of the multiple-proton transfer in the solid state. Transfer is facilitated and occurs concertedly in the cyclic dimers and trimers of substituted triazoles. Such structures are also possible, although they have not yet been reliably identified for other azoles except imidazoles. Proton transfers in solution involve participation of one or several molecules of a solvent bound with azole(s) by hydrogen bonds. Inclusion of molecule(s) of a solvent into a rearranging azole associate can fit its structure for spacial requirements, i.e., linearity or limited bending of the hydrogen bond bridges in which proton transfers may occur.

3. *Exocyclic Substituents*

The conclusions about the influence of azole ring substituents on the tautomeric equilibria are summarized in Table VIII. Although sufficient data are available for pyrazoles and imidazoles, it is difficult to correlate them within any well-defined scheme. The energy differences between pairs of tautomers are generally quite small and attempts to analyze these using, for example, the Taft–Topson model failed [95JCR(S)172]. In the case of monosubstituted compounds, Hammet-type equations

$$\text{Pyrazoles:} \quad \log(\mathbf{2a/2b}) = \rho\sigma_{\mathrm{m}} \ (\rho > 1) \tag{3}$$

$$\text{Imidazoles:} \quad \log(\mathbf{14a/14b}) = 4.5\ \sigma_{\mathrm{m}} \tag{4}$$

retain practical interest [76AHC(S1)]. For the general case of substitution in pyrazoles R^3 = or ≠ H, (Eq. 5) correlates results reasonably well for solutions in dipolar aprotic solvents:

$$\log K_T = \mathrm{a}\Sigma_{3,5}\sigma_{\mathrm{J}} + \mathrm{b}\Sigma_{3.5}\sigma_{\mathrm{R}}. \tag{5}$$

TABLE VIII
TRENDS IN RELATIVE STABILITY OF ANNULAR TAUTOMERS OF AZOLES

Azole	Parent	Substituted
Pyrazole	Equivalent	1. π-Acceptor group prefers 3-position 2. σ-Acceptor group (NH_3^+, CF_3) prefers 5-position. 3. Alkyl group prefers 5-position. 4. Preferential annelation of saturated rings is at 3,4-positions.
Indazole	1H > 2H in the gas phase, solution, and solid state	Substituents do not affect predominance of the 1*H* tautomer
Imidazole	Equivalent	Electron-withdrawing group prefers 4-position
Benzimidazole	Equivalent	$K_T = 1$ is little affected by substitution in the benzene ring
1,2,3-Triazole	2H > 1H gas phase 1H ~ 2H solution	—
Benzotriazole	2H > 1H gas phase 1H > 2H solution 1H > 2H solid	—
1,2,4-Triazole	1H > 4H	Electron-releasing group prefers 5-position Electron-withdrawing group prefers 3-position
Tetrazole	2H > 1H gas phase 1H > 2H solution 1H > 2H solid	Electron-releasing and aryl substituents stabilize the 1*H* tautomer

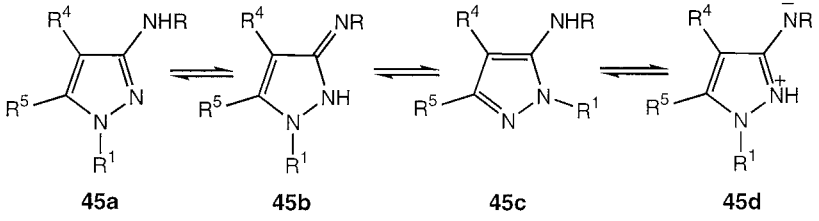
4. *Migratory Aptitudes of Various Groups*

Numerous data on kinetics of annular tautomerism have been obtained for the degenerate rearrangements of pyrazole derivatives. Since all these rearrangements were found to be intramolecular, we can compare kinetic measurements carried out in different media. The following order of increase in migration ability of various groups is established:

$$\text{Aryl} < \text{C(O)R} < \text{Si(OEt)}_3 < \text{SiMe}_3 < \text{GeMe}_3 < \text{BR}_2 < \text{H} < \text{SnBu}_3 \sim \text{HgPh}.$$

II. Side-Chain Tautomerism

This type of tautomerism pertains to azole systems which contain exocyclic amino, hydroxy, thiol, and other proton donor groups.



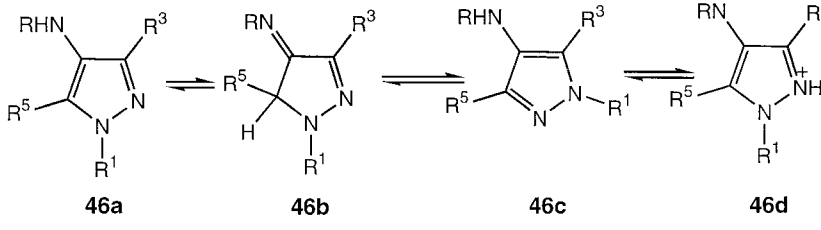
SCHEME 27

A. AMINOAZOLES AND AMINOBENZAZOLES

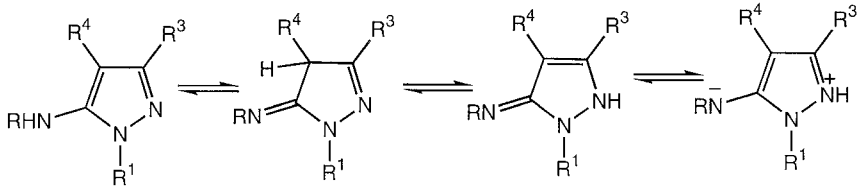
1. *N,N-Containing Azoles*

a. *Aminopyrazoles and Aminoindazoles.* In the case of 3-aminopyrazole **45,** an equilibrium involving four potential tautomers is conceivable. For the majority of the compounds of this series the sole tautomeric form observed has the structure **45a** (Scheme 27) [76AHC(S1), pp. 422, 423, 445; 79OMR587; 84CHEC-I(5)1; 84CHEC-I(5)167; 95JCS(P2)1875; 96CHEC-II(3)1]. However, recently it was shown that the tautomeric equilibrium in 5-aryl-substituted 3-aminopyrazoles **45** (R^5 = 4-X-C_6H_4) depends strongly on the nature of the X substituent: strong electron-withdrawing substituents shift the equilibrium from **45a** to **45c.** For example, when X = H, OMe, or Cl, only **45a** tautomers were detected in the crystal structures by X-ray analysis, while with X = NO_2 only tautomer **45c** was found (97T10783).

Likewise for 4-aminopyrazoles **46** and 5-aminopyrazoles **47** (Scheme 28), the most stable tautomer possesses either the amino structure **46a** [76AHC(S1), pp. 425, 445; 98H(49)157] or **47a** [76AHC(S1), pp. 420, 444; 84CHEC-I(5)167; 96CHEC-II(3)1]. X-Ray structural analysis revealed that the parent 4-aminopyrazole exists in the solid state in two polymorphic forms of amino tautomer **46a;** these forms differ only by the conformation of the NH_2 group [98H(49)157].



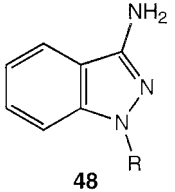
SCHEME 28



47a 47b 47c 47d

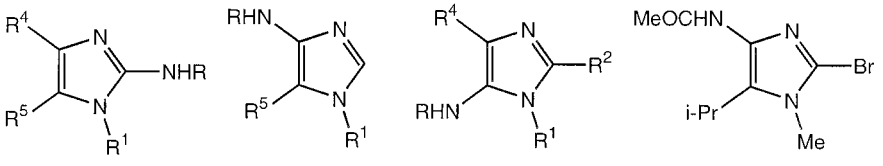
SCHEME 28 (*Continued*)

According to IR-spectroscopic studies, 3-aminoindazole **48** (R = H) and its *N*-benzyl derivative exist exclusively in the amino forms **48** [76AHC(S1), p. 424].



48

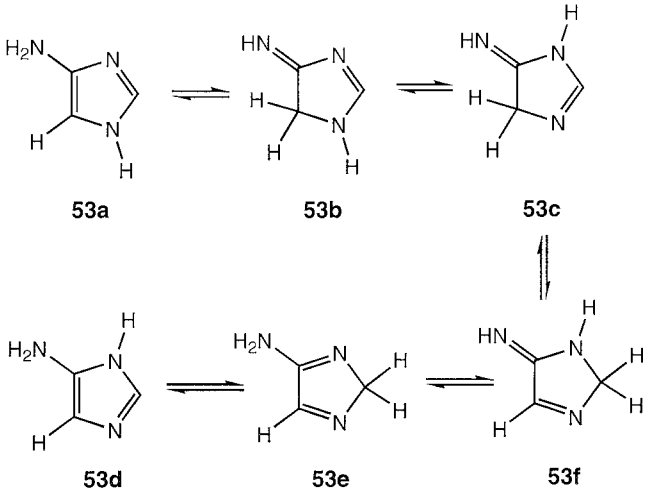
b. *Aminoimidazoles and Aminobenzimidazoles.* Amino tautomers **49**–**52** are the only observable species for most 2-aminoimidazoles **49** [76AHC(S1), pp. 429, 443, 444; 84CHEC-I(5)345] and also for 4- and 5-aminoazoles **50**–**52** [71JCS(B)976].



49 50 51 52

An apparent exception is 2-amino-1-methyl-4,5-diphenylimidazole **49** (R = H, R^1 = Me, R^4 = R^5 = Ph) for which an equilibrium content of about 0.03% of the imino tautomer was detected in a methanol solution by the use of UV spectroscopy [84CHEC-I(5)345].

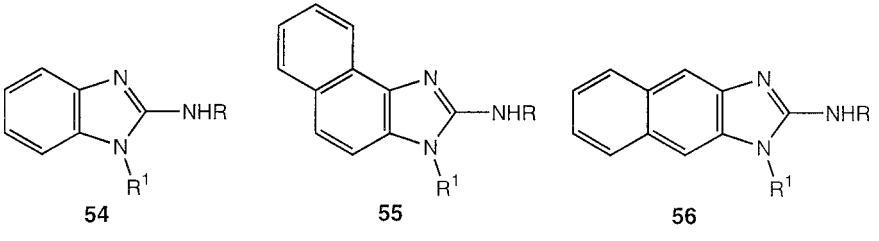
These findings accord with the semiempirical AM1 calculations [92JCS(P1)2779] of the heats of formation of all theoretically possible tautomeric forms of 4-aminoimidazole **53.** The most stable are the tautomers **53a** (ΔH_f = 213 kJ mol^{-1}) and **53d** (ΔH_f = 215 kJ mol^{-1}) (Scheme 29). All



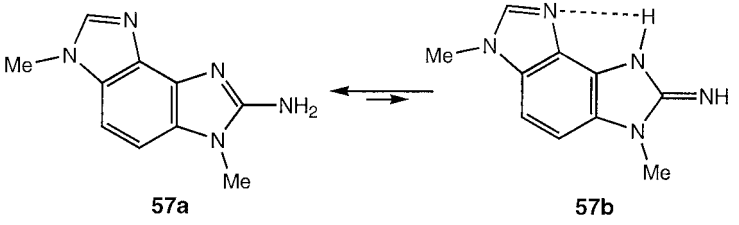
SCHEME 29

other forms are 42 kJ mol^{-1} or more higher in energy than **53a/53d.** There is no ^1H NMR evidence for the existence of tautomeric forms other than **53a** and **53d** in DMSO-d_6 solution [92JCS(P1)2779].

No minor tautomers were detected for 2-aminoimidazoles fused with benzo and naphtho rings **54–56** [76AHC(S1), p. 430; 84CHEC-I(5)345; 96CHEC-II(3)77].

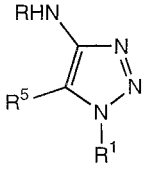


Even in tricyclic bis-imidazole **57,** for which the potential imino-tautomer **57b** would be stabilized by the intramolecular N-H···N bond, the only observable form is the amino tautomer **57a** (Scheme 30) [73KGS807; 76AHC(S1), p. 431].

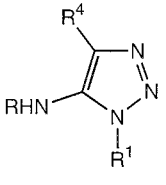


SCHEME 30

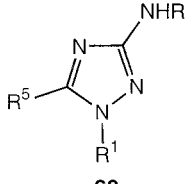
c. *Aminotriazoles.* The structure of a wide series of aminotriazoles **58–63** has been studied and the significant energy preference of their amino-tautomeric forms confirmed [76AHC(S1), p. 439].



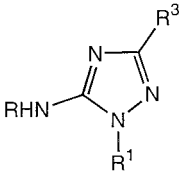
58



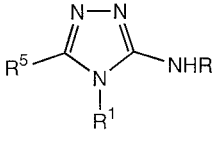
59



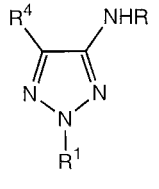
60



61

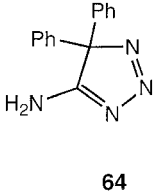


62

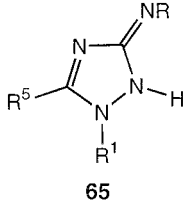


63

The nonaromatic amino structure **64** was found by X-ray and by UV and ^{1}H, ^{13}C, and ^{15}N NMR studies (93CB103) to exist as such both in the solid and solution.



64

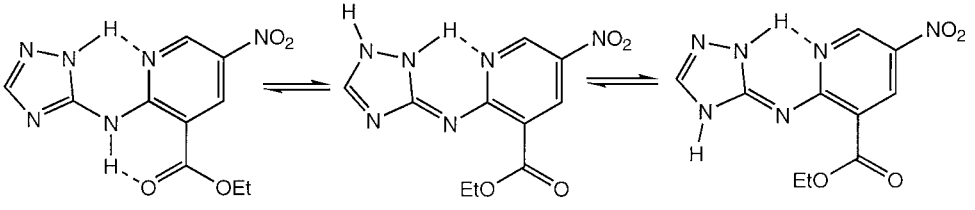


65

Whereas most 3-amino-1,2,4-triazoles prefer the amino form **60** [76AHC (S1), p. 439, 445; 80KGS1414], strong electron withdrawing substituents can lead to the predominance of the imino form, as is the case of the compound **65** (R = C_3F_7) (80KGS1414) or to 5-amino tautomer **61** (R = H, R^3 = CF_3) [98AX(C)442]. This conclusion was based on gas-phase IR and mass-spectroscopic studies.

5-Amino-1,2,4-triazole **61** (R = R^1 = R^3 = H) [76AHC(S1), pp. 439, 444], its 3-nitro-derivative **61** (R = R^1 = H, R^3 = NO_2) (98MRC343), and 2(5)-amino-1,3,4-triazole **62** [76AHC(S1), pp. 439, 444, 76TL3747] all exist as amino forms.

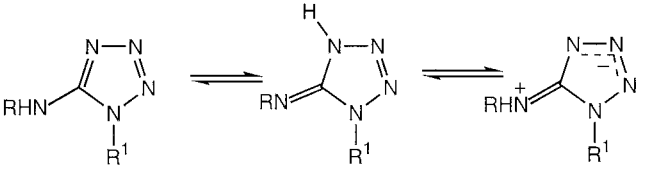
The amino form **66a** of 5-pyridylamino-1,2,4-triazole stabilized by two intramolecular hydrogen bonds is the only tautomer observed by the X-ray study of the crystal (90KGS1632). However in DMSO-d_6, DMF-d_7, and HMPA-d_{18} solutions, the equilibrium involves three tautomeric forms **66a–66c** (Scheme 31) (90KGS1632).



SCHEME 31

d. *Aminotetrazoles.* Prototropic tautomerism of 5-amino-1,2,3,4-tetrazoles can involve an equilibrium of three forms [72MI101; 76AHC(S1), p. 441; 77AHC(21)323; 84CHEC-I(5)791; 91H329; 96CHEC-II(4)621].

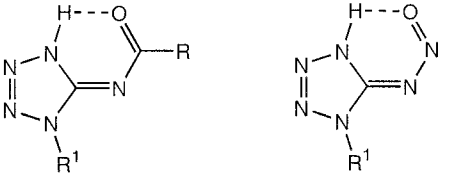
Semiempirical quantum mechanical calculations, X-ray crystallography, laser Raman spectroscopy [72MI101], IR [76AHC(S1), p. 441], and ^1H and ^{13}C NMR studies in solutions of DMSO [77AHC(21)323] and $CDCl_3$ (83M65) point to the energy preference of the amino tautomers **67a** (Scheme 32). A conclusion that the imino form **67b** (R = R^1 = H) predominates in DMF-d_7 solution and occurs in detectable amounts in solutions of CCl_4 and toluene made on the basis of IR and ^1H NMR-spectroscopic studies (92ZOR1767) has been criticized [96CHEC-II(4)621]. However, strong electron-withdrawing substituents R = $COCF_3$, $ArSO_2$ [76AHC(S1), p. 442], and NO_2 [84KGS1569] can shift the tautomeric equilibrium to the imino form **67b.** Tautomeric form **67b** may also be stabilized



67a **67b** **67c**

SCHEME 32

in the acyl **68** [77AHC(21)323] and nitroso **69** [76AHC(S1), p. 443] derivatives owing to formation of intramolecular hydrogen bonds.

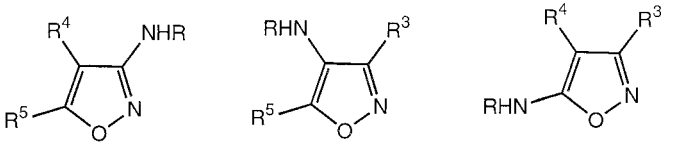


68 **69**

As was concluded (97MI84), many other factors that may affect the position of the amino–imino tautomerism of aminotetrazoles remain to be elucidated.

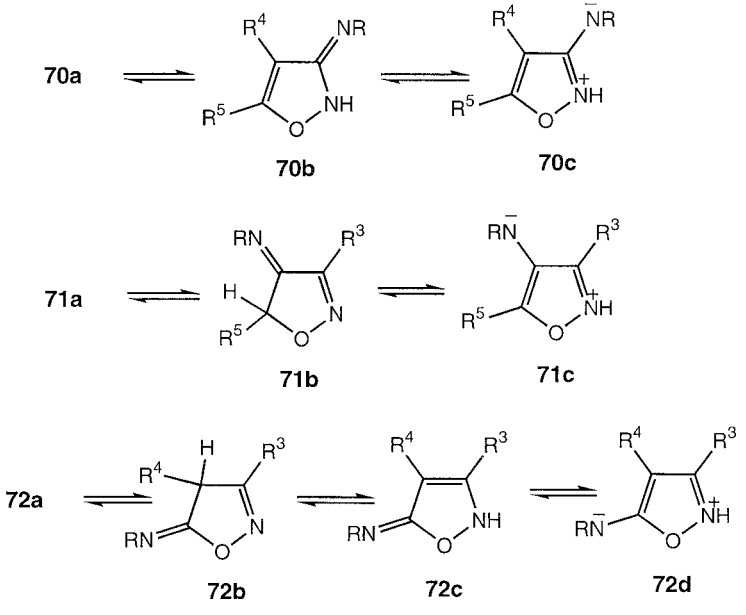
2. *N,O-Containing Azoles*

a. *Aminoisoxazoles and Aminobenzisoxazoles*



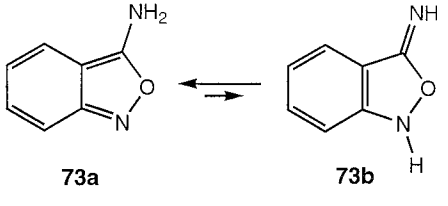
70a **71a** **72a**

An amino group may take any of three possible positions in the five-membered isoxazole ring, giving rise to three tautomeric forms for **70** and **71** and four forms for **72** [76AHC(S1), pp. 416, 444, 445; 84CHEC-I(5)1]. However, only amino structures **70a**–**72a** have been detected using IR- or NMR-spectroscopic techniques (Scheme 33).



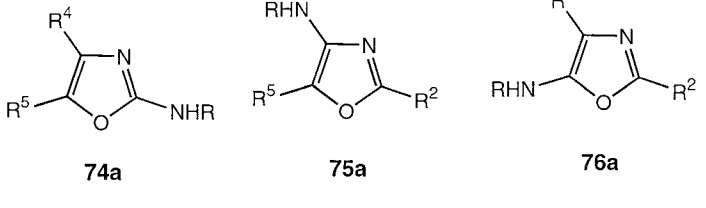
SCHEME 33

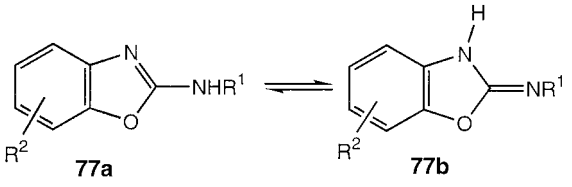
Similarly, the potential equilibrium in solutions of 3-aminobenzisoxazole **73** is fully shifted to the amino isomer **73a** despite the apparent loss of aromaticity (Scheme 34) [76AHC(S1), p. 417].



SCHEME 34

b. *Aminooxazoles and Aminobenzoxazoles.* Only amino isomers **74a**–**76a** were found to be present in solutions of aminooxazoles [72UK877; 76AHC(S1), pp. 425, 431, 444; 84CHEC-I(5)1; 84CHEC-I(6)177; 96CHEC-II(3)261].

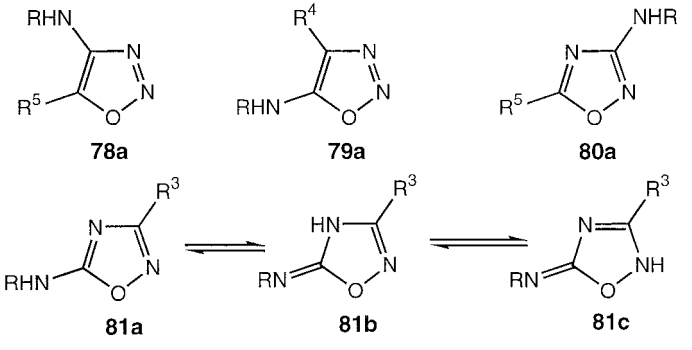




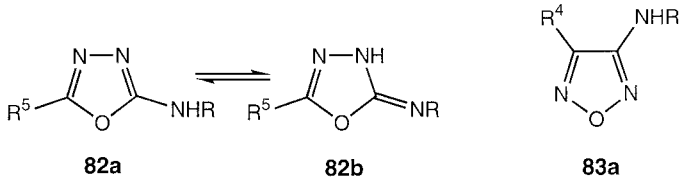
SCHEME 35

For **74a** these findings were corroborated by semiempirical quantum mechanical calculations (81KGS1011) and an X-ray-crystallographic study [81AX(B)2090]. In the case of 2-aminobenzoxazole **77,** the tautomeric equilibrium becomes possible (Scheme 35) [76AHC(S1), p. 426; 79MI424; 81KGS604, 81KGS1011; 84CHEC-I(6)177]. The imino isomer **77b** (R^2 = H, 5-Cl or 5-NO_2) is the stable form in the crystal (73ACS945; 79KGS188; 81KGS604) as dimers stabilized by intermolecular hydrogen bonds (79KGS 188). However, the introduction of electron-withdrawing substituents, such as NO_2 or Br, in the position 6 of the benzoxazole aromatic ring shifts the equilibrium toward amino tautomer **77a.** Thus, 6-nitrobenzoxazoles **77** (R^2 = 6-NO_2, R^1 = alkyl, Ph, $PhCH_2$) and 6-bromo-2-butylaminobenzoxazole **77** (R^1 = *n*-Bu, R^2 = 6-Br) exist in solid state as a mixture of both tautomers (81KGS604). The form **77a** is predominant in $CHCl_3$ solution, its content being increased with increase in concentration of **77** and pH of the solution (79KGS188).

c. *Aminooxadiazoles.* The tautomeric behavior of all the six possible classes of aminooxadiazoles **78–83** has been studied except **78a** and **79a,** which are expected to exist as open-chain structures (Scheme 36). Small amounts of imino forms **81b** and **81c** are present in water and ethanol solutions of **81a,** and small albeit NMR detectable amounts of the imino forms **82b** (R = H, Me, Ph; R^5 = H, Ph) were found in $CDCl_3$ solution [76AHC(S1), pp. 434, 435, 436, 444, 445].



SCHEME 36

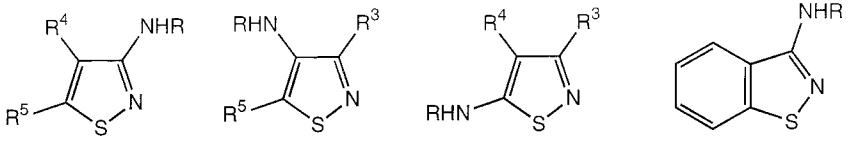


82a **82b** **83a**

SCHEME 36 (*Continued*)

3. *N,S-Containing Azoles*

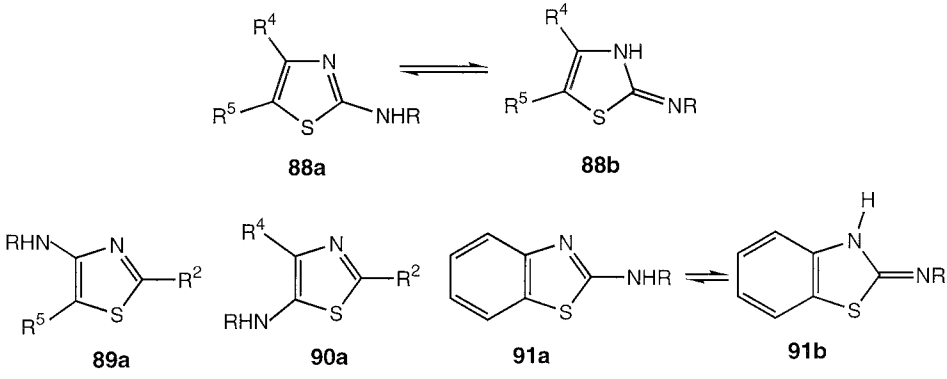
a. *Aminoisothiazoles and 3-Aminobenzisothiazoles.* These compounds exist in solution exclusively as the amino tautomers **84–87** [76AHC(S1), pp. 418, 419, 444, 445; 84CHEC-I(6)131]. See also Scheme 138.



84 **85** **86** **87**

b. *Aminothiazoles and 2-Aminobenzothiazoles.* Whereas 2-aminothiazoles **88** and 2-aminobenzothiazole **91** exhibit amino–imino tautomeric equilibria, 3- and 4-aminothiazoles occur solely as the tautomeric forms **89a** and **90a** (Scheme 37) [72UK877; 76AHC(S1), pp. 427, 428, 444, 445; 84CHEC-I(6)235; 96CHEC-II(3)373]. The amino forms **88a** and **91a** frequently represent the major components of these equilibria [79MI2; 81G159; 82JCS(P2)535; 91KGS1265].

However, the equilibrium amount of the imino tautomers **88b** and **91b** is significantly increased with the increase in the electron-withdrawing ability



88a **88b** **89a** **90a** **91a** **91b**

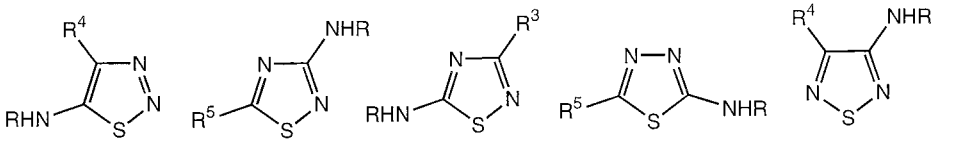
SCHEME 37

of the substituent R [92JHC1461; 94JCS(P2)615; 96CHEC-II(3)373]. This was shown for the compounds **88** with R = $C_6H_2(NO_2)_3$-2,4,6 (92JHC1461); R = Ts [82JCS(P2)535]; R = C(O)R′ [76DOK860; 82JCS(P1)939]; and R = C(S)R′ (88KGS410). X-Ray study [94JCS(P2)615] led to the amide structure **91a** (R = $COCHClCH_3$) for 2-(2′-chloropropioamido)benzothiazole, whereas 2-(2′,2′,2′-trichloroacetamido)benzothiazole exists in the crystal as the imido tautomer **91b** [R = $C(O)CCl_3$].

According to an X-ray crystallographic study, 2-(*N*-phenylamino)thiazole forms in the crystal dimers of the imino tautomers, which are linked together by the intramolecular NH···N bonds [77AX(B)106].

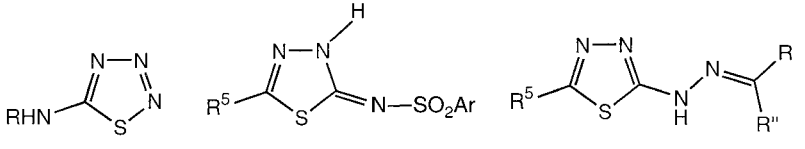
Another factor influencing the position of the amino–imino equilibrium is polarity of the medium [92JHC1461; 94JCS(P2)615]. Thus, in DMSO solution the compounds **88** and **91** exist in the tautomeric forms **88b** and **91b,** which possess higher dipole moments as compared to **88a** and **91a** respectively, the latter being the major isomers in solutions of the less polar solvent CCl_4. Addition of tetrabutylammonium bromide to CCl_4 solutions of **88** and **91** shifts the tautomeric equilibria toward the imino forms (92JHC1461).

c. *Aminothiadiazoles.* For aminothiadiazoles, only amino tautomers **92–96** have been detected [76AHC(S1), pp. 437, 444; 96CHEC-II(4)307].



92 **93** **94** **95** **96**

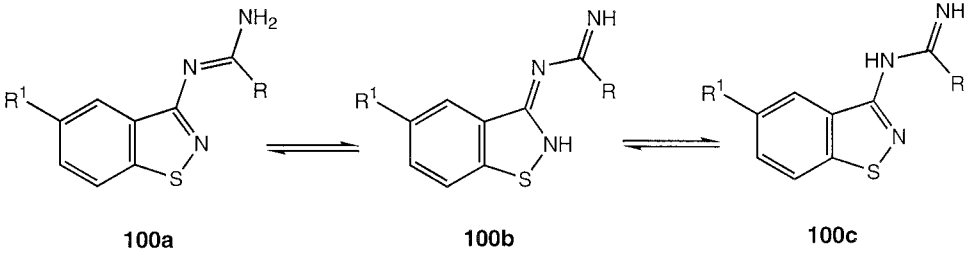
Only amino tautomeric forms were also observed for the derivatives of 5-amino-1,2,3,4-thiatriazole **97** [76AHC(S1), p. 440; 84CHEC-I(6)579].



97 **98** **99**

The possible amino–imino tautomerism of sulfonamides **98** [76AHC(S1), p. 438] and hydrazones **99** [76AHC(S1), p. 438] has been previously discussed.

The tautomeric relationships for benzisothiazolamidines **100** are more complicated (Scheme 38) (95AP217). In the solid, compound **100** (R = Ph, R^1 = H) exists in the amino form **100a,** whereas in a DMSO-d_6 solution at 298 K the tautomers **100b,c** have also been detected using ^{1}H NMR spectroscopy.



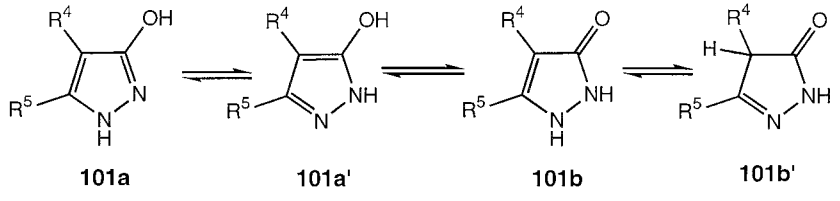
SCHEME 38

B. HYDROXYAZOLES, HYDROXYBENZAZOLES, AND THEIR DERIVATIVES

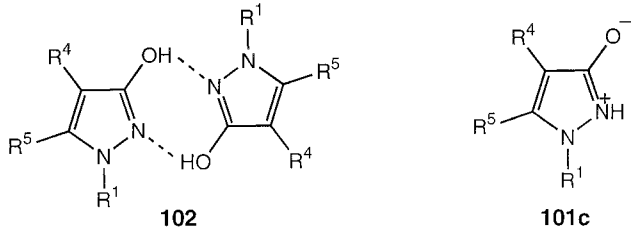
1. *N,N-Containing Azoles*

a. *Hydroxypyrazoles and Hydroxyindazoles.* The prototropic tautomerism of 3-hydroxypyrazoles involves the equilibrium of four isomeric forms (93JA2352; 94JPC11353).

The hydroxy tautomer **101a** predominates in the gas phase, in the solid state [98JCS(P1)2813, 98JST(447)71], and in solutions in nonpolar solvents [76AHC(S1), pp. 339, 389; 84CHEC-I(5)167; 90JCS(P2)195; 92JST(T)217; 94JPC11353; 97MI105] and polar aprotic solvents (such as DMSO) (Scheme 39) [98JCS(P2)2813]. Dimerization **102** stabilizes the 3-hydroxy tautomers [76AHC(S1), p. 342; 98JST(447)71].



SCHEME 39

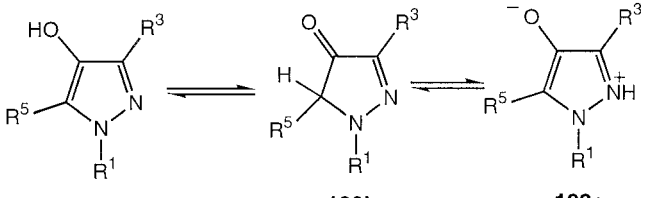


The oxo tautomer **101b** prevails in water and other proton-donor solvents [76AHC(S1), p. 339; 91H329; 93JA2352; 94JPC11353]. The possible participation in solutions in polar solvents of the zwitterionic forms **101c** has been discussed: their relative weight increases with increasing dielectric permittivity of a solvent (91H329).

Tautomeric equilibria of 3-hydroxypyrazole **101** ($R^4 = R^5 = H$) have been thoroughly analyzed by various quantum-chemistry methods [90JCS(P2)195; 91H329; 92MI231; 97MI105] including sophisticated approximations taking account of electron correlation and solvent effects (93JA2352; 94JPC11353). The results are controversial. The MP4/6-31G**//3-21G calculation (93JA2352) suggests the energetic preference of the **101b′** tautomer, but this result seems ambiguous in the light of more detailed calculations (94JPC11353), which showed the extreme dependence of the relative energies of the tautomers on basis set effects and the level at which electron correlation was included. The "best estimate" at the current level of theory was in favor of 10–17 kJ mol^{-1} energy preference for **101a** over other possible tautomeric forms. Accounting for solvent effects in the framework of an SCRF scheme identifies **101b** as the major tautomer in water, in agreement with experimental investigations.

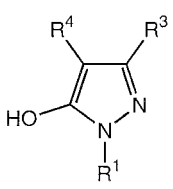
Only the hydroxy form **103a** for 4-hydroxypyrazole was determined in early studies of the tautomeric equilibrium (Scheme 40) [76AHC(S1), pp. 357, 389; 76CJC1752]. More recent investigations into the structure of type **103** compounds revealed the existence in the equilibrium of the additional tautomers **103b** and **103c,** with **103c** predominant [85MI121; 90JCS(P2)195; 91H329].

Eight prototropic tautomers are formally possible for N-unsubstituted pyrazol-5-one **104** ($R^1 = R^3 = R^4 = H$) [76AHC(S1), p. 346; 97T5617]. However, the equilibria observed usually involve only three of them [72UK877; 76AHC(S1), pp. 313, 326, 388; 76JPR555; 96ZOB1341; 97AQ219, 97T5617].

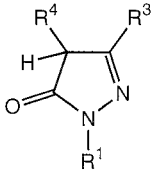


103a **103b** **103c**

SCHEME 40



104a

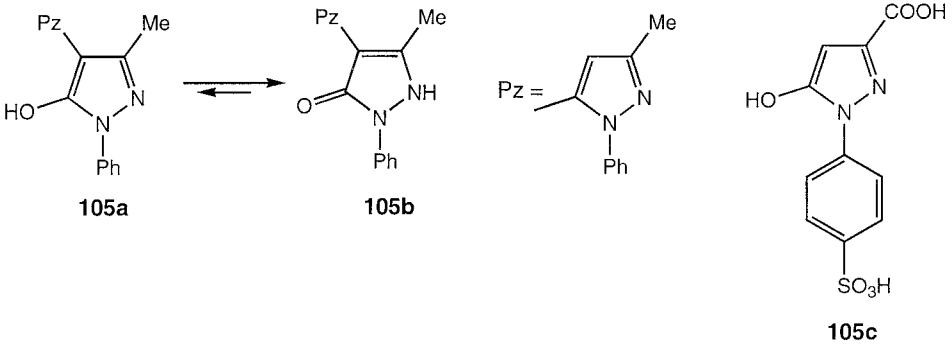


104b

104c

Conclusions as to the relative importance of the tautomeric forms of pyrazolones are rather controversial. In general, the HC-CO form **104b** prevails in nonpolar solvents, while the HN-CO form **104c** is favored in polar ones [72UK877; 76AHC(S1), p. 326, 76TL2245; 77JCS(P2)1024; 80ZN(B)1019; 82JPR827; 84CHEC-I(5)167; 89ZNK2966; 91KGS355; 92MI595; 93BSB735; 95T4891; 96CHEC-II(3)1, 96ZOB1341, 96ZOR1346; 97T5617]. Some evidence was also presented for substantial equilibrium amounts of the hydroxy form **104a** (92MI595). This tautomeric equilibrium is temperature dependent: the percentage of CH tautomer **104b** significantly increases with increasing temperature [99JCS(P2)211]. In the solid state, most tautomerizable pyrazolin-5-ones exist either in the hydroxypyrazole form **104a** or in the HN-CO form **104c;** the latter is preferred since it is stabilized by intermolecular hydrogen bonds NH···O=C (93BSB735). Thus, it was shown that 3-methylpyrazolin-5-one [71AX(B)1227], 1-(4′-bromophenyl)-3-methylpyrazolin-5-one (97AQ219), and pyrazole **105** (95T4891) all crystallize as HN-CO tautomers **104c** ($R^1 = R^4 = H$, $R^3 = Me$), **104c** (R^1 = aryl, $R^3 = Me$, $R^4 = H$), and **105b,** respectively (Scheme 41).

The equilibrium in pyrazolin-5-ones, containing one or more carboxylate or sulfonate group, is extremely sensitive to the pH of the medium. For example, pyrazolinone **105c,** which exists in D_2O solution at pH 2 as an enol

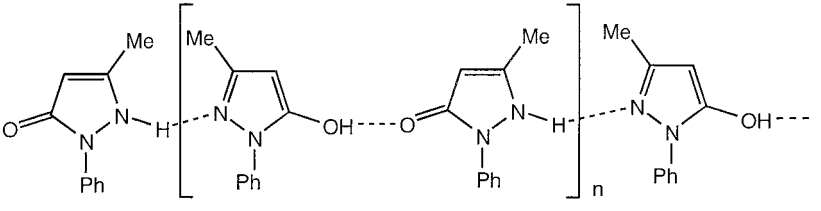


105a **105b** **105c**

SCHEME 41

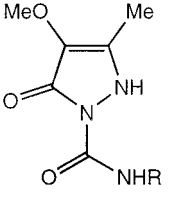
dianion, on basification converts into the corresponding NH-oxo form. The latter predominates at pH ≥ 4.5 (91JHC641).

Tautomeric forms **104a** and **104c** are both present in the crystal of 1-phenyl-3-methylpyrazolin-5-one (R^1 = Ph, R^3 = Me, R^4 = H) in the polymeric structure **106** (97AQ219). Interestingly, the introduction of electron-withdrawing substituents into the 1-phenyl ring significantly affects the equilibrium. Thus, 1-(2′,4′-dinitrophenyl)-3-methyl-2-pyrazolin-5-one, in contrast to other 1-arylpyrazolin-5-ones, exists in the solid state, in $CDCl_3$ solution, and in the gas phase as CH tautomer **104b** (R^1 = 2,4-$(O_2N)_2C_6H_3$, R^3= Me, R^4= H) (98NJC1421).

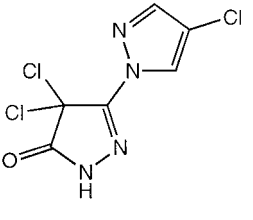


106

X-Ray crystal structure determinations of 1-(aminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2H)-one **107** (R = H) and 1-(phenylaminocarbonyl)-3-methyl-4-methoxy-1*H*-pyrazol-5(2H)-one **107** (R = Ph) demonstrated that both molecules exist in the crystal exclusively as NH-CO tautomers (97T5617). The tautomeric form similar to **104b** is realized in the crystal of 4,4-dichloro-substituted pyrazolone **108** (93BSB735).



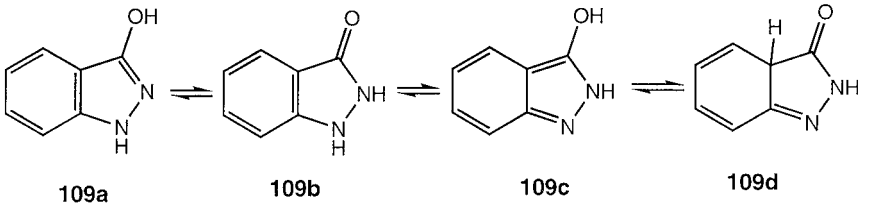
107



108

Of four possible tautomeric forms of indazolinone-3 **109,** evidence for the existence of solely the nonaromatic isomer **109b** in the solid state has been obtained (Scheme 42) [76AHC(S1), p. 352; 96CHEC-II(3)1, 96JCS(P2) 2263].

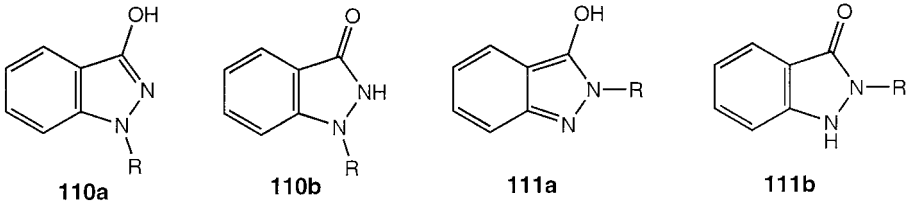
An early IR study (60JCS3278) indicated the existence of the tautomer



SCHEME 42

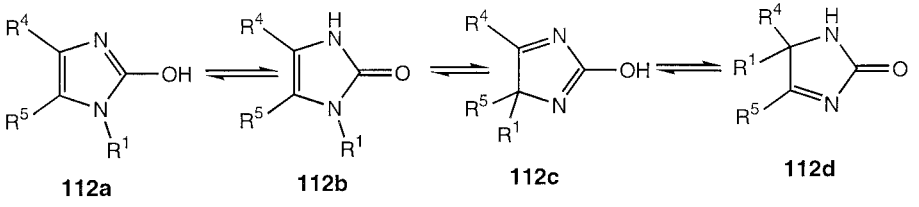
109b in the solid state, and this conclusion was confirmed by a crystal structure determination [86JCS(P2)1677]. The tautomer **109b** predominates in solutions of proton-donor solvents (water, methanol, ethanol, CF_3CH_2OH) [85MRC784; 96JCS(P2)2263]. However, according to ^{13}C and ^{15}N NMR studies the major tautomer (75–85%) is **109a** in DMSO [86JCS(P2)1677; 96JCS(P2)2263]. The equilibrium amount of **109c** is very small, its proportion being estimated as ca. $10^{-4.7}$ [96JCS(P2)2263].

1-Substitution produces a switch to type **110a** tautomers [76AHC(S1), p. 352; 84CHEC-I(5)167]. This effect was attributed, on the basis of AM1 calculations [96JCS(P2)2263], to an enforced molecular planarity leading to strong (R)NNH lone-pair repulsion in tautomers **110b.**



No definite experiments have been carried out with regard to the relative stability of the tautomers of 2-substituted indazolones **111.** On the basis of basicity arguments, the hydroxy tautomer **111a** was considered to be preferred [96JCS(P2)2263].

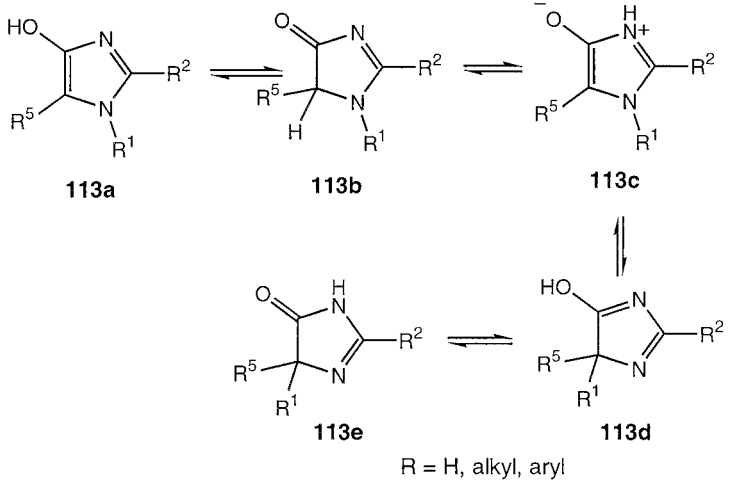
b. *Hydroxyimidazoles and Hydroxybenzimidazoles.* According to the numerous UV, IR, and NMR spectroscopic studies [76AHC(S1), pp. 361, 388; 84CHEC-I(5)1, 84CHEC-I(5)345; 96CHEC-II(3)77, 96JST227] corroborated by semiempirical quantum mechanical calculations, the oxo tautomer **112b** is the major form for N-unsubstituted imidazolyl-2-ones (R^1 = H) (Scheme 43) . For N^1-substituted **112** (R^1 = Alk, Br) the equilibrium is restricted to two forms, **112a** and **112b,** the latter being favored [76AHC(S1), p. 361].



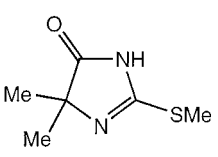
SCHEME 43

Five isomeric forms may, in principle, be involved in the prototropic tautomeric equilibrium of imidazolyl-4-ones **113** (R^1 = H), their number being reduced to three in the case of N-substitution (R^1 = Alk, Ar) [84CHEC-I(5)345].

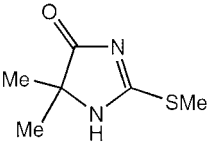
An ^1H and ^{13}C NMR study (71BSF1040; 76BSB579) identified the oxo form **113b** as the major tautomer in deuteroacetic acid (82% of **113b** and 18% of **113a**) and trifluoroacetic acid (80% of **113b** and 20% of **113a**) (Scheme 44) (71BSF1040; 76BSB579; 91CJC383). The tautomeric constants, K_T = [**113a**]/[**113b**], were also determined for a solution of **113** ($R^1 = R^5$ = Me, R^2 = Ph) in mixed solvents: 1.22 (CD_3CN/CF_3COOH, 2:1) and 3.0 (CD_3COCD_3/CF_3COOH, 2:1). In DMSO/CF_3COOH = 2:1, **113** ($R^1 = R^5$ = Me, R^2 = Ph) exists exclusively as hydroxy tautomer **113a.** The oxo form **114**(Δ^1) prevails in a benzene solution of 2-methylthio-5,5-dimethylimidazolin-4-one, which is in accord with the results of MNDO, PM3, and AM1 calculations and X-ray crystal structure determination (91CJC383).



SCHEME 44



114 (Δ^1)



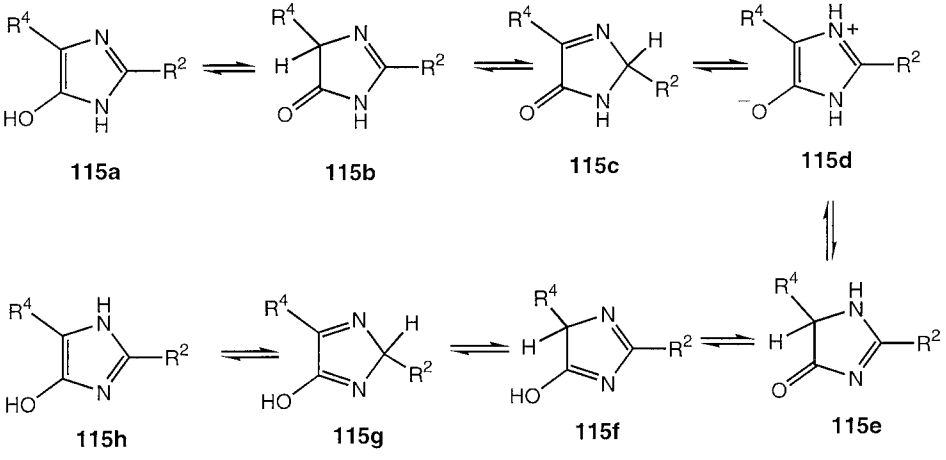
114 (Δ^2)

The prototropic tautomerism of 5-hydroxyimidazoles **115** may involve eight possible forms for N^1-unsubstituted and four forms for N^1-substituted compounds (Scheme 45).

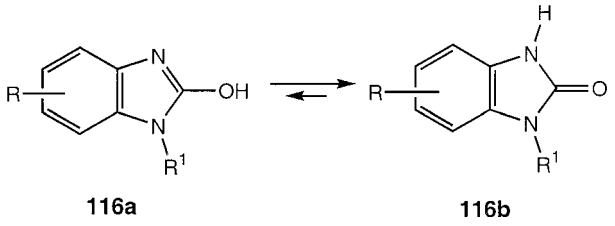
In the gas phase and in solution the oxo tautomer **115b** is the energetically favorable form [76AHC(S1), pp. 374, 388; 79BSB289; 84CHEC-I(5)345, 84LA831; 96CHEC-II(3)77]. Isomer **115c** was originally considered as a less stable form with no chance of being experimentally observed (79BSB289), although later the predominance of **115c** ($R^2 = R^4 = H$) in DMSO-d_6 solution was suggested on the basis of ^1H NMR spectra [84LA831]. The same conclusion was extended to the mesoionic structure **115d,** even though implications on its role in the tautomeric equilibrium were made [71BSF1040; 96CHEC-II(3)77].

For 2-hydroxybenzimidazole, the oxo tautomer **116b** is considered as a dominant form in equilibrium (Scheme 46) [76AHC(S1), p. 361].

Little information is available on the tautomeric equilibrium of *N*-hydroxyimidazoles **117** and *N*-hydroxybenzimidazoles **118** in solution



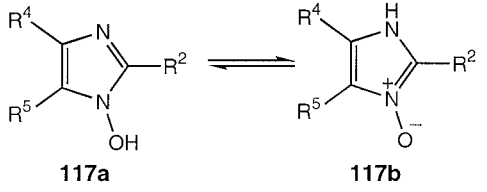
SCHEME 45



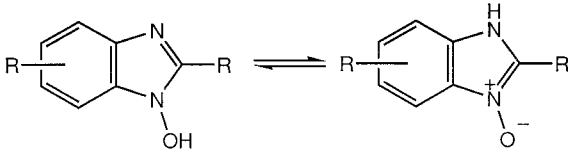
116a **116b**

SCHEME 46

[76AHC(S1), p. 485; 84CHEC-I(5)345], except that for both types of compounds the *N*-oxide forms **117b** and **118b** predominate in proton donor solvents (Scheme 47).



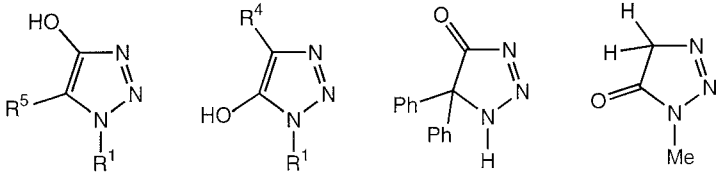
117a **117b**



118a **118b**

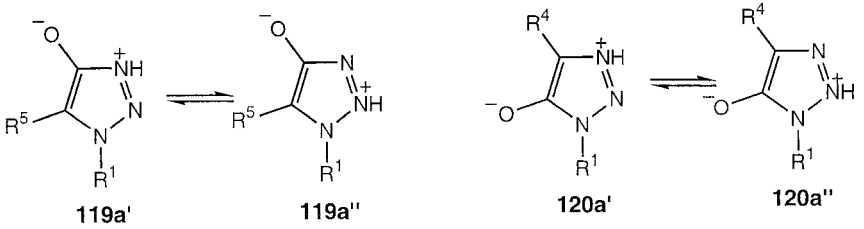
SCHEME 47

c. *Hydroxytriazoles and Hydroxybenzotriazoles*



119 **120** **121** **122**

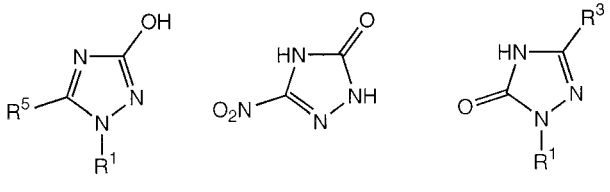
4- and 5-Hydroxy-1,2,3-triazoles usually prefer the hydroxy isomeric forms **119** and **120** respectively [76AHC(S1), pp. 383, 384, 388, 389; 90BSB1007]. However, in solution, the coexistence of small amounts of zwitterionic forms **119a′, 119a″, 120a′, 120a″** was also discussed (Scheme 48)



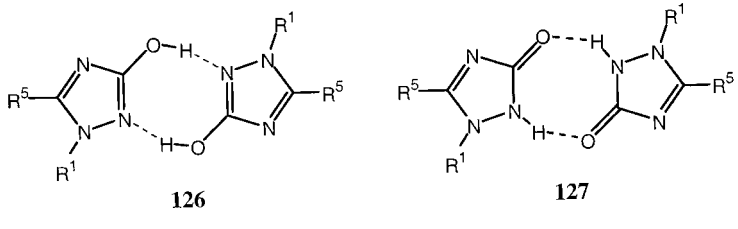
SCHEME 48

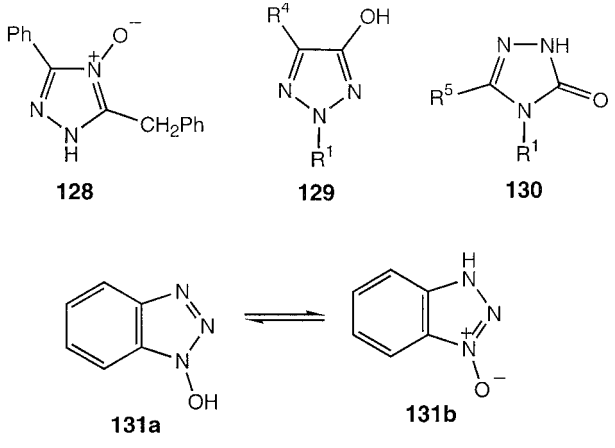
[76AHC(S1), pp. 384, 385]. For some derivatives of **119** and **120,** the relative stability of oxo isomers may be enhanced. Thus, the predominance of the 5,5-diphenyldihydro-4*H*-1,2,3-triazol-4-one structure **121** in solution has been confirmed by UV and ^{13}C and ^{15}N NMR studies (93CB103). Also, 1-methyl-5-hydroxy-1,2,3-triazole exists mainly in the tautomeric form **120** (R^1 = Me, R^4 = H) [76AHC(S1), p. 385], although the existence of a minor amount of oxo form **122** was postulated to explain the exchange of the 4-position proton in D_2O.

Most 3-hydroxy-1,2,4-triazoles exist in the hydroxy form **123** [76AHC(S1), pp. 377, 389; 84CHEC-I(5)733]. An exception is the 5-nitro derivative, which in the solid state possesses the oxo structure **124** (97JPC3605).



Type **125** oxo forms are characteristic for 5-hydroxy-1,2,4-triazoles [76AHC(S1), pp. 379, 388]. These forms are additionally stabilized by an electron-withdrawing substituent, R^3 = NO_2 (98MRC343). Both hydroxy and oxo tautomers are capable of forming stable dimers owing to the intermolecular hydrogen bonds (**126** and **127** [76AHC(S1), pp. 377, 379).



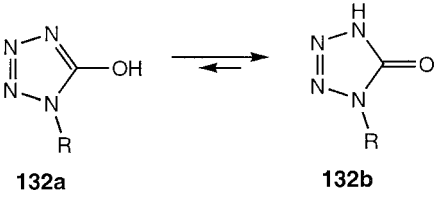


SCHEME 49

For *N*-hydroxy-1,2,4-triazole, the zwitterionic structure **128** was suggested [89AX(C)782, 96CHEC-II(4)127]. Whereas N^1-substituted 3-hydroxy-1,2,5-triazoles prefer the hydroxy form **129,** 2-hydroxy-1,3,4-triazoles exist as oxo forms **130** (Scheme 49) [76AHC(S1), pp. 380, 383, 388, 389].

The tautomerism of 1-hydroxybenzotriazole **131** has been studied in detail [83AX(C)1089; 95SA(A)1801]. The *N*-oxide form **131b** dominates in aqueous solution, whereas **131a** is the major tautomer in organic solvents (methanol, ethanol, acetone, DMF, DMSO) (80OMR339; 85MRC181; 86AG381). In agreement with quantum mechanical calculations (92JOC3698), the photoelectron spectrum of **131** confirms the energy preference of **131a** in the gas phase [95SA(A)1801].

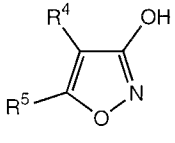
d. *Hydroxytetrazoles.* The oxo tautomer **132b** is the predominant form in the equilibrium (Scheme 50) [76AHC(S1), pp. 386, 388; 84CHEC-I(5)791; 86BCJ3263; 96CHEC-II(4)621]. The oxo structure **132b** of the parent hydroxytetrazole (R = H) in the solid state was unambiguously established by X-ray crystallographic studies [98AX(C)1160].



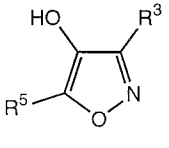
SCHEME 50

2. *N,O-Containing Azoles*

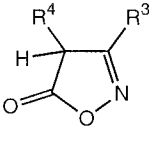
a. *Hydroxyisoxazoles and Hydroxybenzisoxazoles.* 3-Hydroxyisoxazoles and 4-hydroxyisoxazoles usually exist in solution as the hydroxy tautomeric forms **133a** and **134a** respectively [76AHC(S1), pp. 308, 355, 388, 389; 84CHEC-I(6)1; 90JCS(P2)195; 91H329; 96CHEC-II(3)221]. However, there are indications that the NH-oxo form of 3-hydroxyisoxazole **133c** (R^4 = R^5 = H) predominates in organic nonpolar solvents (90T1975).



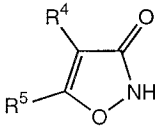
133a



134a



135b

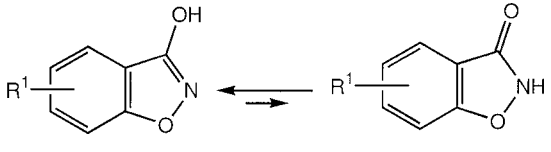


133c

135c

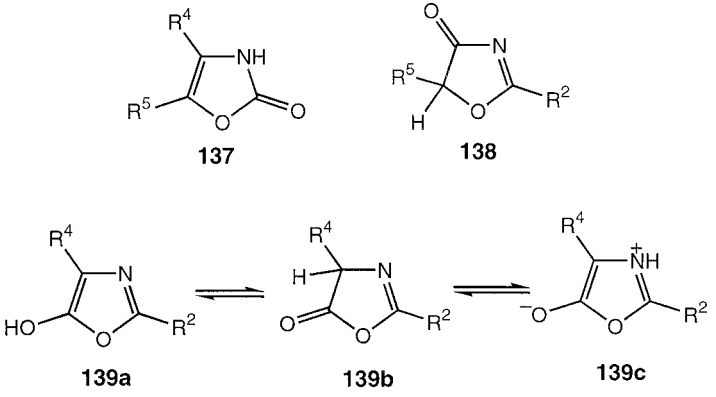
In aqueous solution and in the gas phase, the CH-oxo form **135b** (R^4 = H) of 5-hydroxyisoxazole prevails over the NH-oxo tautomer **135c** (R^4 = H) and the hydroxy form [72UK877; 76AHC(S1), p. 300; 77OMS65; 79AHC(25)147; 84CHEC-I(6)1; 85MI121; 96CHEC-II(3)221, 96MI653]. This result is in accord with predictions based on large basis set quantum mechanical calculations accounting for electron correlation and utilizing the SCRF model of solvent effects [90JCS(P2)195; 91H329; 92JCS(P2)2151; 93JA8810, 93JCS(P2)1771; 97MI105].

In the prototropic equilibrium, 3-hydroxybenzisoxazole exists exclusively as hydroxy tautomer **136a** (Scheme 51) [76AHC(S1), p. 310].



136a **136b**

SCHEME 51

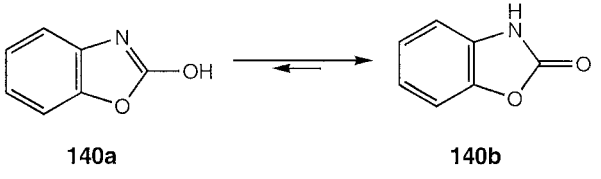


SCHEME 52

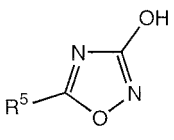
b. *Hydroxyoxazoles and Hydroxybenzoxazoles.* The oxo forms **137** and **138** are confirmed to be the predominant tautomers of 2-hydroxyoxazole [76AHC(S1), pp. 360, 388, 389; 84CHEC-I(6)177; 85MI121; 90JCS(P2)195; 91H329; 96CHEC-II(3)261] and 4-hydroxyoxazole [84CHEC-I(6)177; 85MI121; 90JCS(P2)195; 91H329] respectively (Scheme 52).

In the tautomeric equilibria of 5-hydroxyoxazoles, the oxo tautomer **139b** and(or) the mesoionic tautomer **139c** are considered to be the major forms [76AHC(S1), p. 388; 91H329]. However, with increase in solvent polarity the contribution of the hydroxy form **139a** increases [84CHEC-I(6)177]. Infrared- and ^{1}H NMR-spectroscopic studies [76AHC(S1), p. 360] and X-ray structural investigation (73ACS945) demonstrated unambiguously the 1,3-benzoxazolone-2 structure **140b** for 2-hydroxy-1,3-benzoxazole (Scheme 53).

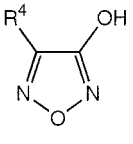
c. *Hydroxyoxadiazoles.* Only the hydroxy forms were reported for 3-hydroxy-1,2,4-oxadiazoles **141** [76AHC(S1), pp. 376, 389; 84CHEC-I (6)365; 96CHEC-II(4)179] and 3-hydroxy-1,2,5-oxadiazoles **142** [76AHC (S1), pp. 381, 389; 96CHEC-II(4)229].



SCHEME 53

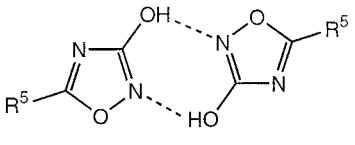


141

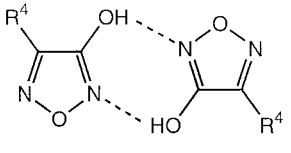


142

The formation of dimers **143** [76AHC(S1), p. 376; 84CHEC-I(6)365; 96CHEC-II(4)179] or **144** [76AHC(S1), p. 382] contributes to the stabilization of these hydroxy tautomers.



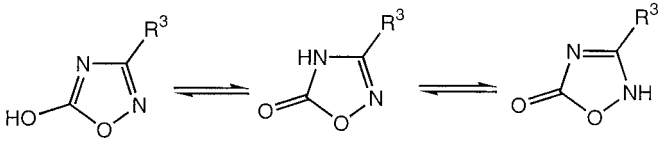
143



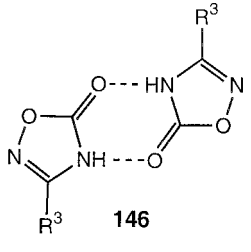
144

For 5-hydroxy-1,2,4-oxadiazoles, equilibria with dominant oxo forms **145b** prone to type **146** dimerization were observed (Scheme 54) [76AHC(S1), p. 378; 76BSB35; 84CHEC-I(6)365; 96CHEC-II(4)179].

Simple 1,2,3-oxadiazoles are unknown (spontaneous ring opening to give diazoketones) and hence 4-hydroxy- **147** and 5-hydroxy-1,2,3-oxadiazoles **148** are not studied (Scheme 55). For 2-hydroxy-1,3,4-oxadiazoles, the oxo tautomers **149b** are usually considered the major forms [84CHEC-I(6)427, 96CHEC-II(4)267].

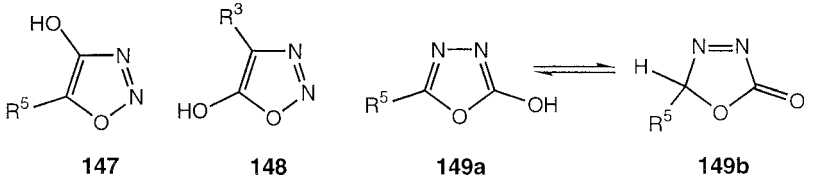


145a **145b** **145c**



146

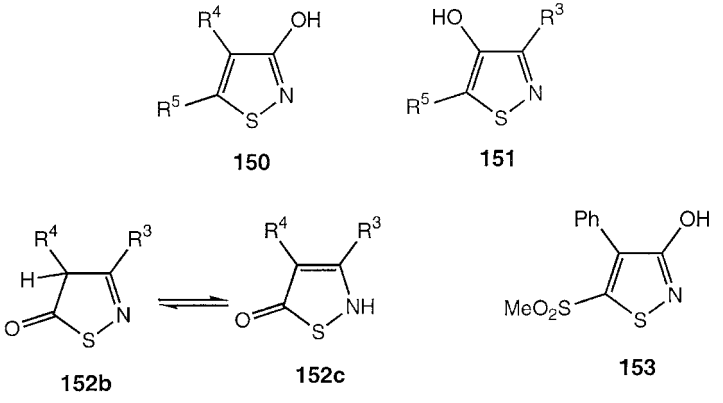
SCHEME 54



SCHEME 55

3. *N,S-Containing Azoles*

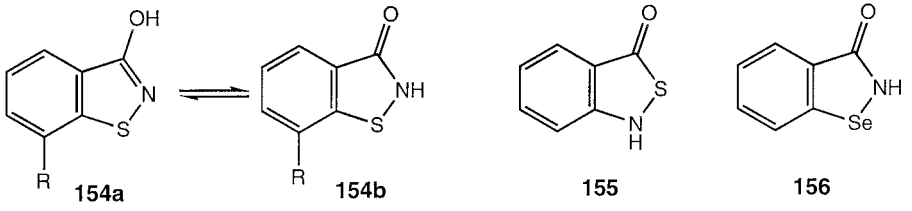
a. *Hydroxyisothiazoles, Hydroxybenzothiazoles, and Their Derivatives.* 3- and 4-Hydroxyisothiazoles **150** and **151** exist as such (Scheme 56) [76AHC(S1), pp. 312, 356; 84CHEC-I(6)131; 85MI447; 96CHEC-II(3)319]. In contrast, 5-hydroxyisothiazole in solution forms an equilibrium mixture of the oxo isomers **152b** and **152c** [76AHC(S1), pp. 311; 81AQ(C)105; 84CHEC-I(6)131; 96CHEC-II(3)319]. The hydroxy structure of the 3-hydroxyisothiazole **153** was proven by X-ray analysis [77JCS(P2)1332].



SCHEME 56

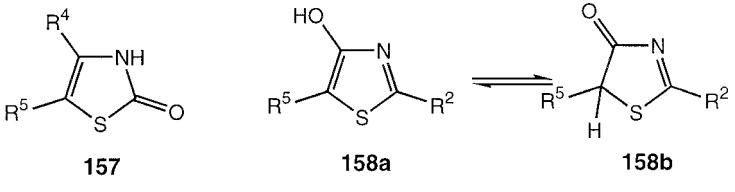
The tautomeric equilibrium between the hydroxy, **154a,** and oxo, **154b,** forms of 1,2-benzisothiazolin-3-one is shifted to the right (Scheme 57) [76AHC(S1), p. 312; 81G71; 84CHEC-I(6)131]; a conclusion supported by X-ray structural determinations of some derivatives of **154:** e.g., R = Cl [69AX(B)2349].

The oxo tautomers are also the stable forms of 2,1-benzisothiazol-3-one **155** [73CB376; 75AJC129; 76AHC(S1), p. 311; 84CHEC-I(6)131] and 1,2-isoselenazol-3-one **156** (91CZ135).



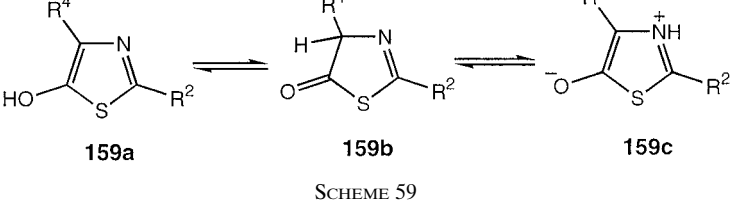
SCHEME 57

b. *Hydroxythiazoles, Hydroxybenzothiazoles, and Their Derivatives.* 2-Hydroxythiazole and its derivatives exist in the oxo form **157** [76AHC (S1), pp. 361, 388; 84CHEC-I(6)235; 96CHEC-II(3)373], whereas the 4-hydroxythiazoles **158** exist in solution as an equilibrium of the hydroxy and oxo forms [76AHC(S1), pp. 369, 388; 86AKZ685]. According to X-ray study (86AKZ688), a derivative of **158** (R^2 = Me, R^5 = Ph) has the hydroxy structure **158a** in the crystal (Scheme 58).



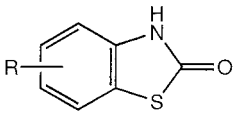
SCHEME 58

For 5-hydroxythiazoles **159** an equilibrium involving the hydroxy, **159a,** oxo, **159b,** and the zwitterionic, **159c,** forms was discussed (Scheme 59) [76AHC(S1), p. 367].

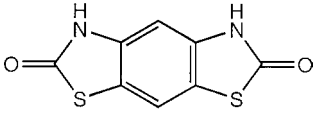


SCHEME 59

2-Hydroxybenzothiazole **160** and its derivatives, **161, 162,** and Se-analog **163,** all exist exclusively in their oxo forms [76AHC(S1), p. 361; 93SC621; 96CHEC-II(3)493].



160



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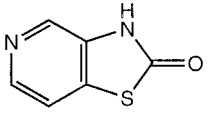

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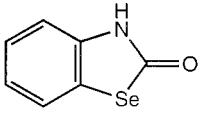
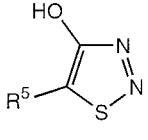
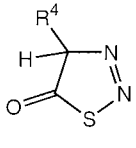


163

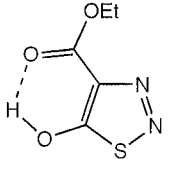
c. *Hydroxythiadiazoles.* Although the prototropic tautomerism of 4-hydroxy- and 5-hydroxy-1,2,3-thiadiazoles has not yet been investigated, by analogy with the corresponding thiazoles one can expect stabilization of the hydroxy form **164** and the oxo form **165.** However, compound **166** exists in the hydroxy form, which is evidently stabilized by the intramolecular hydrogen bond [76AHC(S1), p. 384].



164

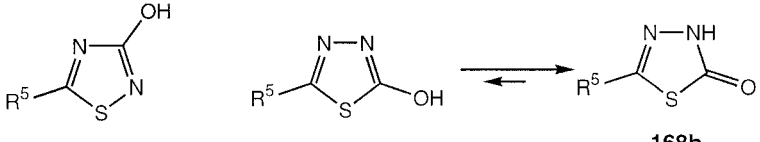


165



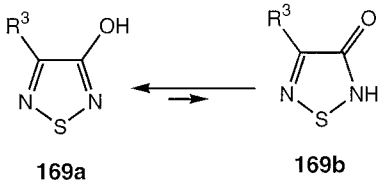
166

The hydroxy tautomers are also the predominant forms of 3-hydroxy-1,2,4-thiadiazoles **167** (Scheme 60) [76AHC(S1), pp. 377, 389; 79JHC961; 84CHEC-I(6)463; 96CHEC-II(4)307]. For 2-hydroxy-1,3,4-thiadiazoles **168** [96CHEC-II(4)379] and 3-hydroxy-1,2,5-thiadiazoles **169,** equilibria between the hydroxy and the NH-oxo forms were reported [76AHC(S1), pp. 382, 389]. As shown by ^{13}C NMR studies, the NH-oxo tautomer **168b** (R^5 = H) predominates in $CDCl_3$ solution (84BSB559).



167 168a 168b

SCHEME 60



169a **169b**

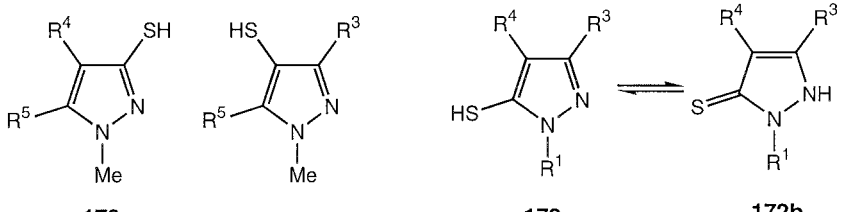
SCHEME 60 (*Continued*)

C. MERCAPTOAZOLES, MERCAPTOBENZAZOLES, AND THEIR DERIVATIVES

1. *N,N-Containing Azoles*

a. *Mercaptopyrazoles and Mercaptoindazoles.* The photoelectron spectra of 1-methyl-3-mercaptopyrazoles **170** demonstrate their mercapto tautomeric form (83CJC1197; 96UK326). Possible tautomerism in 4-mercaptopyrazoles **171** has not been studied (Scheme 61).

For 5-mercaptopyrazoles, solvent-dependent equilibria between the mercapto, **172a,** and the thione, **172b,** tautomers were observed [76AHC(S1), pp. 393, 414; 77BSB949; 84CHEC-I(5)167; 96CHEC-II(3)1, 96UK326]. As shown by UV and ^{1}H NMR spectra (77BSB949), dioxane solution of **172** (R^1 = R^3 = Me, R^4 = H) contains only the mercapto tautomer **172a;** in DMSO, the content of the thione form **172b** is equal to 70%, whereas in solution of protic solvents **172b** reaches 100%. The photoelectron spectrum of **172** indicates **172a** to be the favored tautomer in the gas phase (83CJC1197).

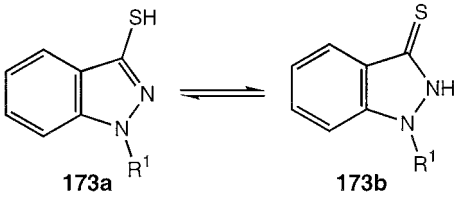


170 **171** **172a** **172b**

SCHEME 61

The mercapto, **173a,** and the thione, **173b,** forms coexist in solutions of some 3-mercaptoindazoles (Scheme 62) [76AHC(S1), p. 395; 84CHEC-I(5)167; 96CHEC-II(3)1].

Infrared and ^{1}H NMR spectra show that for the *N*-benzyl derivative the mercapto tautomer **173a** (R^1 = CH_2Ph) is preferred in chloroform solution, while in the solid this compound exists as the thione **173b** [76AHC(S1), p. 395].

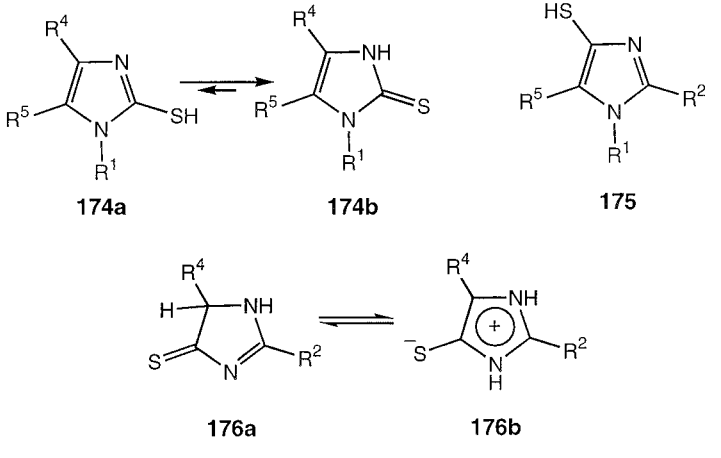


SCHEME 62

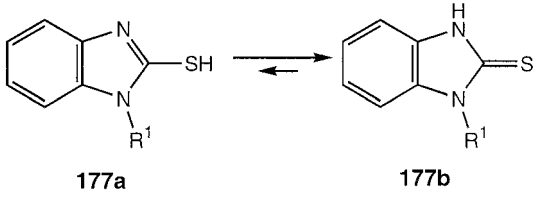
b. *Mercaptoimidazoles and Mercaptobenzimidazoles.* For 2-mercaptoimidazoles, the thiol–thione tautomeric equilibrium is shifted completely to the thione form **174b** both in solution and in the solid (Scheme 63) [74T3831; 76AHC(S1), pp. 400, 414; 84CHEC-I(5)345; 85MRC166; 87SA(A) 501; 88KGS1587]. A contrary conclusion claiming the predominance of the thiol form **174a** in the solid state (89CCC2045) on the basis of the SH region of the IR spectra of **174a** is of doubtful validity in view of known uncertainties in assignments of the low-intensity SH vibrations (88MI643; 96UK326).

No information on the tautomeric behavior of 4-mercaptoimidazoles **175** is available [76AHC(S1); 84CHEC-I(5)345; 96CHEC-II(3)77; 97JCS(P1)2983].

As shown by an ^{1}H NMR study (77BSB967), *N*-methyl derivatives of 5-mercaptoimidazole exist in the thione form **176a** in chloroform. According to results obtained in (82KGS957), the zwitterionic form **176b** should not be excluded from consideration for the compounds **176** (R^4 = $CONH_2$, $CSNH_2$).



SCHEME 63

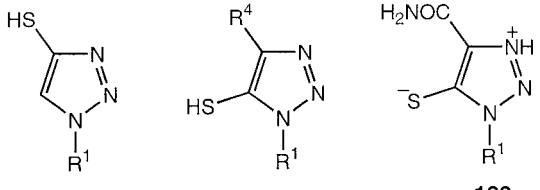


177a **177b**

SCHEME 64

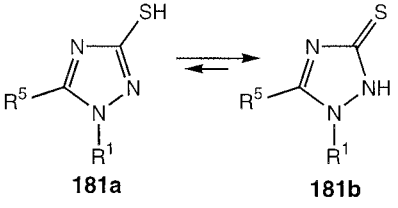
The thione tautomer **177b** is the predominant form of 2-mercaptobenzimidazoles **177** both in solution [76AHC(S1), p. 401] and in the solid state (Scheme 64) [76AX(B)345].

c. *Mercaptotriazoles, Mercaptobenzotriazoles, and Their Derivatives.* It was usually presumed that 4-mercapto- and 5-mercapto-1,2,3-triazoles **178** and **179** exist in their thiol forms [76AHC(S1), pp. 409, 410, 414, 415; 90BSB1007]. However, a recent X-ray study (93BSB1) demonstrated the zwitterionic forms, e.g., **180,** in the crystal.



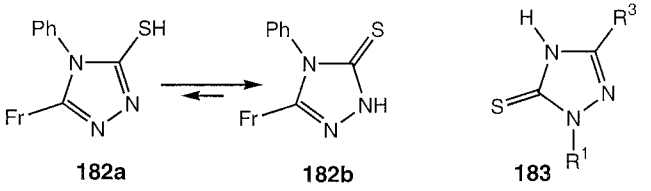
178 **179** **180**

In solutions of 3-mercapto-1,2,4-triazoles the tautomeric equilibrium is shifted to the thione forms **181b** (Scheme 65) [76AHC(S1), pp. 404, 415; 96UK326]. Such an equilibrium was observed for 3-mercapto-5-ferrocenyl-4-phenyl-1,2,4-triazole **182** (94MI1121; 96UK326). The thione tautomers **183** of 5-mercapto-1,2,4-triazoles are predominant [76AHC(S1), pp. 405, 414; 97SA(A)699].



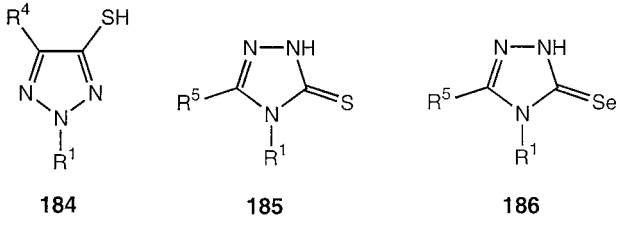
181a **181b**

SCHEME 65

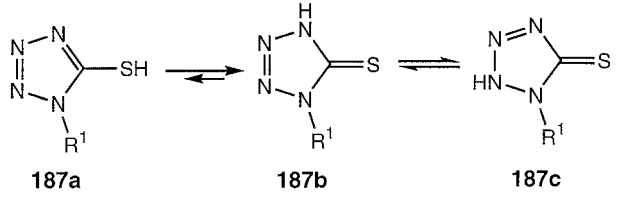


SCHEME 65 (*Continued*)

The tautomerism of 3-mercapto-1,2,5-triazole **184** has not been studied thus far. Very little information is available on the structure of 2-mercapto-1,3,4-triazole and its selenium analog, but apparently the thione **185** and selenone **186** forms are preferred for these compounds [76AHC(S1), pp. 408, 414].



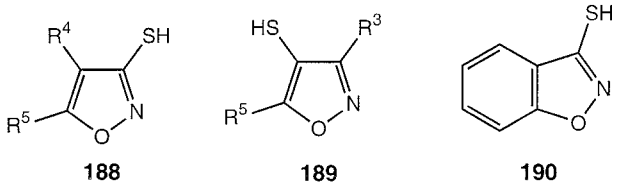
d. *Mercaptotetrazoles.* 2-Mercaptotetrazole exists in a thione form, most probably **187b** (Scheme 66) [74JOC3770; 76AHC(S1), pp. 412, 414; 76JOC1875; 84CHEC-I(5)791; 85JOC2794; 85MRC166, 86BCJ3263; 96CHEC-II(4)621, 96UK326], but possibly **187c** (86BCJ3263; 96UK326).



SCHEME 66

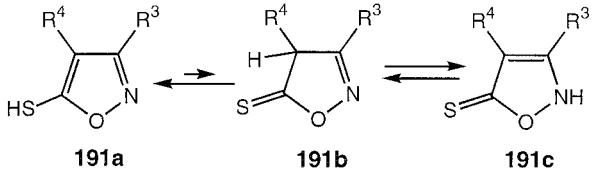
2. *N,O-Containing Azoles*

a. *Mercaptoisoxazoles.* The tautomerism of 3-mercapto- and 4-mercaptoisoxazoles **188** and **189** and 3-mercaptobenzisoxazole **190** is virtually unstudied [76AHC(S1), pp. 391, 415; 84CHEC-I(6)1; 96CHEC-II(3)221, 96UK326].



188 **189** **190**

Early work on the tautomerism of 5-mercaptoisoxazoles **191** (67JHC54) suggested the predominance of the thiol form **191a** in equilibrium with small amounts of the thione tautomers (Scheme 67).

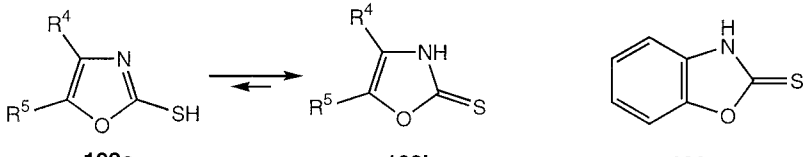


191a **191b** **191c**

SCHEME 67

b. *Mercaptooxazoles and Mercaptobenzoxazoles.* Tautomeric equilibria in solutions of 2-mercaptooxazoles are shifted to the thione forms **192b** (Scheme 68) [74T3831; 76AHC(S1), pp. 397, 414; 96UK326]. This is also true for 2-mercaptobenzoxazole **193** [76AHC(S1), p. 397; 83H1713].

The strong energy preference of **192b** ($R^4 = R^5 = H$) over its mercapto form **192a** was estimated as 44 kJ mol^{-1} by MNDO calculations (88CJC2835).

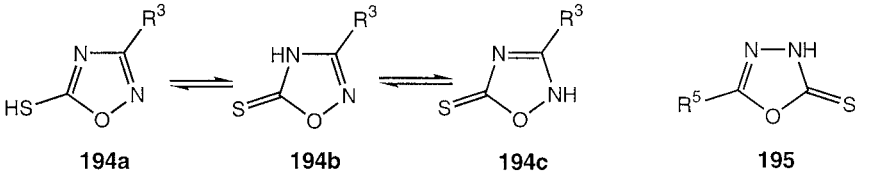


192a **192b** **193**

SCHEME 68

c. *Mercaptooxadiazoles.* The mercapto tautomer **194a** and the thione tautomer **194c** are considered to be the dominant forms at equilibrium (Scheme 69) [76AHC(S1), pp. 404, 414].

Based on IR and ^{13}C NMR-spectroscopic studies [76AHC(S1), pp. 406, 414; 94MI1027; 96CHEC-II(4)267], 2-mercapto-1,3,4-oxadiazole prefers the thione form **195.**

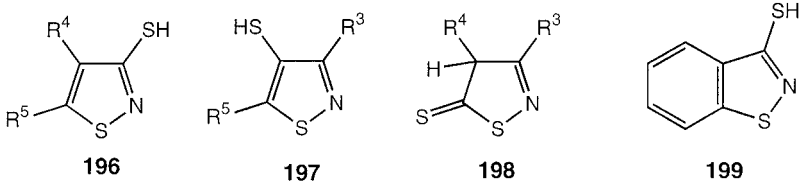


194a 194b 194c 195

SCHEME 69

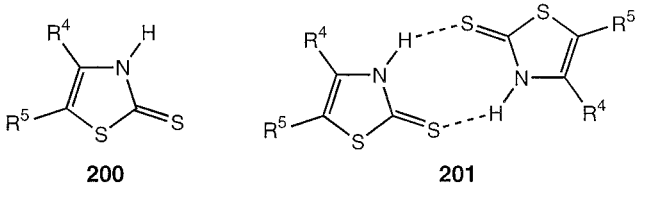
3. *N,S-Containing Azoles*

a. *Mercaptoisothiazoles and Mercaptobenzisothiazoles.* Only 3-mercaptoisothiazole and its derivatives **196** have been studied thus far. These compounds exist as thiols [76AHC(S1), pp. 392, 415; 81AQ(C)105; 84CHEC-I(6)131; 96CHEC-II(3)319]. No data are available on the possible thiol–thione tautomerism of compounds **197–199** [76AHC(S1), pp. 415, 416; 96CHEC-II(3)319, 96UK326].



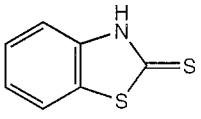
196 197 198 199

b. *Mercaptothiazoles and Mercaptobenzothiazoles.* 2-Mercaptothiazole and its derivatives strongly prefer the thione tautomeric form **200** [76AHC(S1), pp. 398, 414; 84CHEC-I(6)235; 89CCC2045; 96CHEC-II(3)373; 96UK326], which derives additional stabilization in solution by the formation of dimers **201** (89CCC2045). Semiempirical quantum mechanical calculations (88CJC2835; 96UK326) of the relative stabilities of the tautomers of **200** ($R^4 = R^5 = H$) agree with the experimental data.

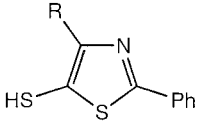


200 201

The thione form **202** is also characteristic of 2-mercaptobenzothiazole [76AHC(S1), p. 399], whereas the thiol tautomer was found to be the preferred form of 2-phenyl-5-mercaptothiazole **203** (76T583).

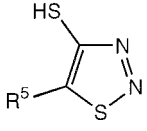


202

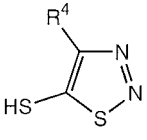


203

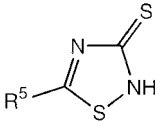
c. *Mercaptothiadiazoles and Mercaptothiatriazole.* No studies on the tautomerism of 4-mercapto-1,2,3-thiadiazoles **204** and 5-mercapto-1,2,3-thiadiazoles **205** have been carried out. For 3-mercapto-1,2,4-thiadiazoles, the thione tautomers **206** are usually considered as the predominant forms [76AHC(S1), pp. 403, 415].



204

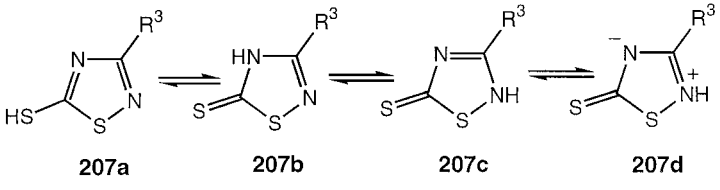


205



206

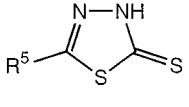
A similar conclusion has also been reached in the case of 5-mercapto-1,2,4-thiadiazoles **207** [76AHC(S1), pp. 405, 414; 96CHEC-II(4)307] although the question remains open of which of the three possible thione forms is the energetically favored tautomer (Scheme 70).



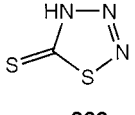
207a **207b** **207c** **207d**

SCHEME 70

The thione tautomers **208** and **209** exist in solutions of 2-mercapto-1,3,4-thiadiazoles [76AHC(S1), pp. 407, 414; 77JOC3725; 80SA(A)517; 91MI637; 96UK326] and 5-mercapto-1,2,3,4-thiatriazole [76AHC(S1), pp. 411, 414; 77JHC1417; 84CHEC-I(6)579] respectively.



208

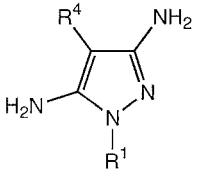


209

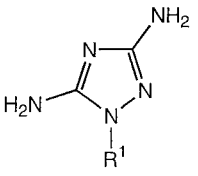
D. Azoles with Two and More Potentially Tautomeric Groups

1. *Diaminoazoles*

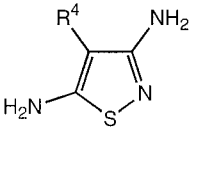
Similarly to aminoazoles, diaminoazoles prefer their amino forms: **210** for 3,5-diaminopyrazole [76AHC(S1), p. 460; 84CHEC-I(5)167; 96CHEC-II(3)1]; **211** for 3,5-diamino-1,2,4-triazole; and **212** for 3,5-diaminoisothiazole [76AHC(S1), p. 460]. The triamino structure **213** was proven by an X-ray crystallographic study of 4-aminoquinazine hydrobromide [73JCS(P2)1].



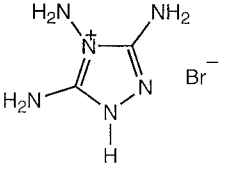
210



211

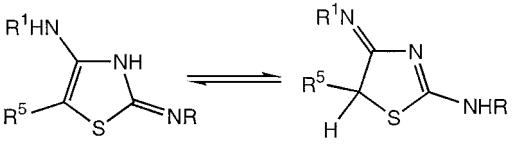


212



213

However, for derivatives of 2,4-diaminothiazole **214** evidence exists for the amino–imino tautomeric equilibrium (Scheme 71) [76AHC(S1), p. 460].

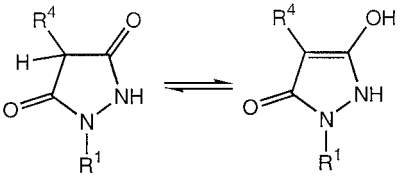


214a **214b**

Scheme 71

2. *Dihydroxyazoles*

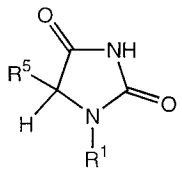
The major tautomer of 3-hydroxypyrazol-5-one is the dioxo form **215a,** but in pyridine **215a** exists in equilibrium with **215b** (Scheme 72) [76AHC (S1), p. 450].



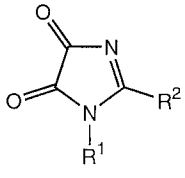
215a **215b**

Scheme 72

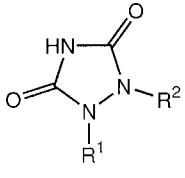
2,4-Imidazolediones [76AHC(S1), p. 453]; 4,5-imidazolediones [76AHC (S1), p. 454]; 3,5-dioxotriazoles [76AHC(S1), p. 455]; and 2,5-dioxo-1,3,4-triazoles [76AHC(S1), p. 356] all exist in the dioxo tautomeric forms, **216**–**219,** respectively.



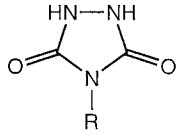
216



217

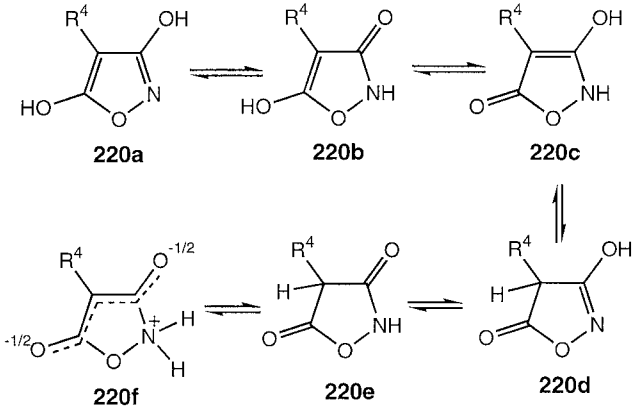


218



219

For 3-hydroxyisoxazol-5-ones **220,** a complex equilibrium involving six potential tautomers was considered [75T1861; 76AHC(S1), p. 449]. In the solid, the tautomeric forms **220b** and **220c** were observed, while in solution (DMSO, chloroform, ethanol) the zwitterionic tautomer **220f** is regarded as the major form (Scheme 73).

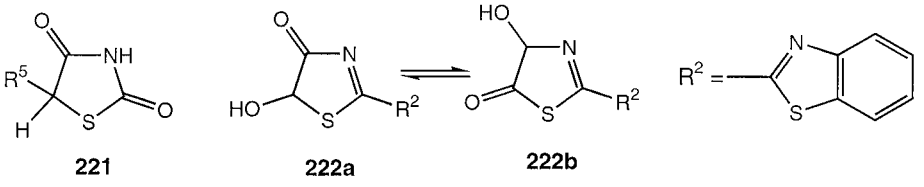


220a **220b** **220c**

220f **220e** **220d**

SCHEME 73

The dioxo tautomer is the major form of thiazole-2,4-dione **221,** whereas thiazole-4,5-diones exist in solution as mixtures of monooxo–monohydroxy tautomers **222a,b** (Scheme 74) [76AHC(S1), p. 453].

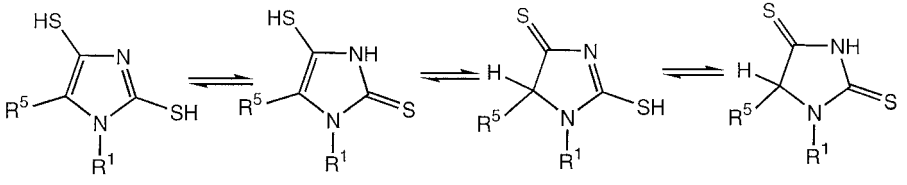


221 **222a** **222b**

SCHEME 74

3. *Dimercaptoazoles*

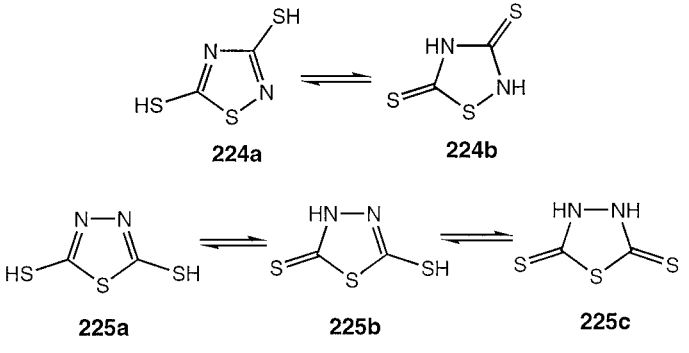
Four prototropic tautomers are possible for unsubstituted 2,4-dimercaptoimidazole. In the absence of detailed studies, the thiol–thione form **223b** is considered to be the major tautomer (Scheme 75) [72CJC2423; 76AHC (S1), p. 457; 84CHEC-I(5)345].



223a **223b** **223c** **223d**

SCHEME 75

Dithione tautomeric form **224b** was identified from IR spectroscopy [76AHC(S1), p. 459; 96UK326] as predominant for 3,5-dimercapto-1,2,4-thiadiazole and its derivatives (Scheme 76).



224a **224b**

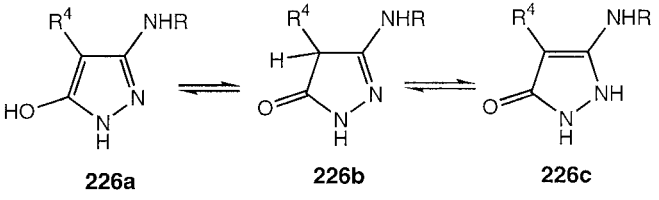
225a **225b** **225c**

SCHEME 76

The tautomeric equilibrium of 2,5-dimercapto-1,3,4-thiadiazole **225** has been intensely studied. Both experimental evidence [76ACS(B)71, 76AHC (S1), p. 458; 76AX(B)2866; 79MI226; 86MI1289; 90JHC139; 93JCS(P2)417; 95CJC1258; 96CHEC-II(4)379, 96UK326] and quantum mechanical (CNDO and RHF/4-31G) calculations [87JST(T)373; 90BCJ2991] point to the mixed thiol–thione structure **225b** as the most stable. This conclusion is corroborated by X-ray determinations of **225** [76AX(B)2866] and its 5-(1-hydroxycyclohexyl) [93JCS(P2)417] and 5-(diethylamino) (95CJC1258) derivatives. An early conclusion on the preference of the dithione tautomer **225c** based on the IR-spectroscopic study (75JINC1804) has been treated as inconclusive (88MI643; 96UK326).

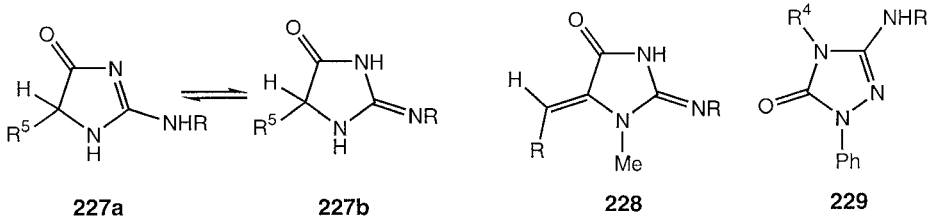
4. *Aminohydroxyazoles*

The tautomeric equilibria of 5-hydroxy-3-aminopyrazoles **226** are affected by the substituent R^4 (Scheme 77) [76AHC(S1), p. 467]. While structure **226b** is usually the major form, for some compounds of type **226** (R = COMe, COPh) the equilibrium content of **226c** may reach 60% (74BSF291).



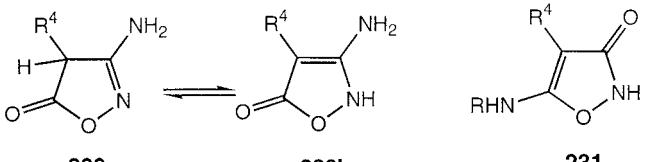
SCHEME 77

2-Iminoimidazolin-4-ones **227b** are the only tautomers detected for 4-hydroxy-2-aminoimidazoles (R = H, Ph; R^5 = H) (91KGS62). Similar tautomeric forms are also characteristic of 1-methyl-2-imino-5-benzylideneimidazole-4-one **228** (91KGS62) and 3-amino-1,2,4-triazol-5-ones **229** (R = R^4 = H, COMe) (Scheme 78) [76AHC(S1), p. 482].



SCHEME 78

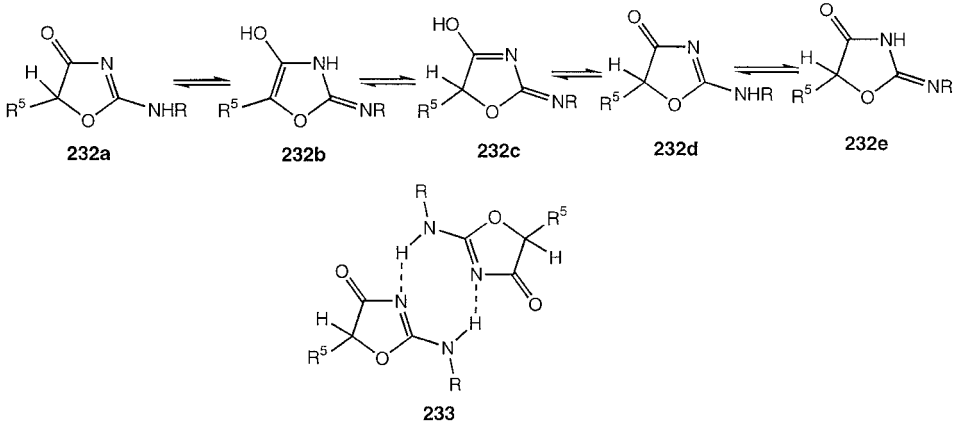
Amino–oxo tautomers are the most stable for 3-amino-5-hydroxyisooxazoles (for which the equilibrium **230a** and **230b** was discussed) and for 5-amino-3-hydroxyisoxazoles, which exist as **231** (Scheme 79) [76AHC(S1), p. 466]. 4-Arylhydrazino-5-hydroxyisoxazoles exist largely in their oxo–hydrazono form [79AHC(25)147].



230a **230b** **231**

SCHEME 79

2-Amino-4-hydroxyoxazoles **232** generally prefer to exist either as the imino–oxo **232e** (R = aryl) (89KGS388) or as the amino–oxo **232d** (R = alkyl) (89KGS388) forms capable of associating in stable eight-membered ring dimers **233** (Scheme 80) [76AHC(S1), pp. 472, 475; 96KGS1011].

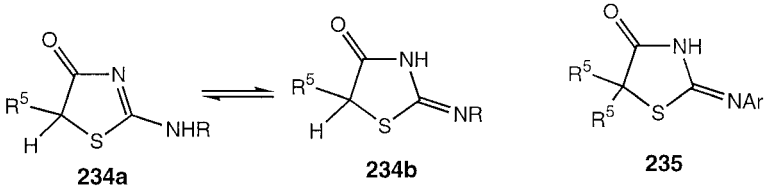


232a **232b** **232c** **232d** **232e**

233

SCHEME 80

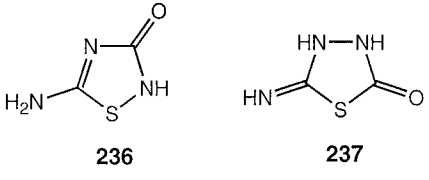
The tautomeric equilibrium of 2-aminothiazolin-4-ones has been well studied [76AHC(S1), p. 476; 78ZOR1327; 85JPR251, 85KGS32; 86KGS544; 94AX(C)1721; 96ZOB1346]. Structure **234a** is considered to be favored (Scheme 81). The parent compound exists as **234a** (R = R^5 = H) in the crystal as shown by X-ray spectroscopy under conditions permitting accurate localization of the mobile proton [94AX(C)1721]. Electron-withdrawing



SCHEME 81

groups R enhance the relative stability of the imino tautomers **234b** (73ZOR412; 78KGS190). The imino structure **235** predominates for 2-aryliminothiazolidin-4-ones (75ZOR1759; 79ZOR1506).

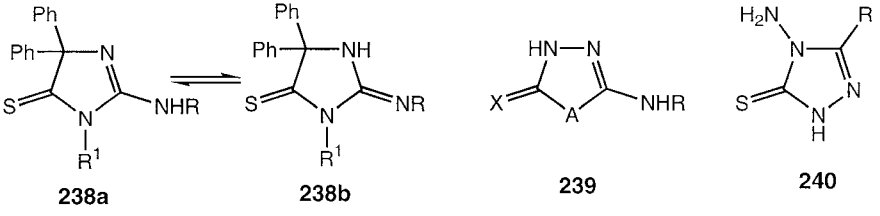
Early IR- and UV-spectroscopic studies [76AHC(S1), p. 481] of 5-amino-1,2,4-thiadiazolin-3-one and 5-amino-1,3,4-thiadiazolin-2-one indicate structures **236** and **237,** respectively.



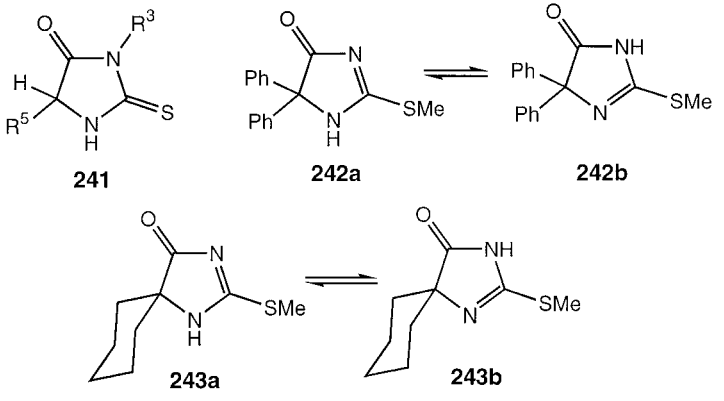
5. *Aminomercaptoazoles*

The tautomeric equilibria of 2-aminoimidazoline-5-thiones **238** are shifted to the imino forms **238b** when R is an electron-withdrawing group (Scheme 82) [96CHEC-II(3)77].

Evidence in favor of the amino–thionic tautomeric form of 2-amino-1,3,4-thiazoline-5-thione **239** (A = X = S; R = H) was obtained from X-ray structural determinations [72AX(B)1584]. A ^{13}C NMR-spectroscopic study (77JOC3725) of compounds **239** (A = Se; X = S; R = Me) demonstrated their amino–thionic structure. A similar tautomeric form **240** is also dominant for the hydrazine derivative (R = NHNHCOPh) [73JCS(P2)4].



SCHEME 82

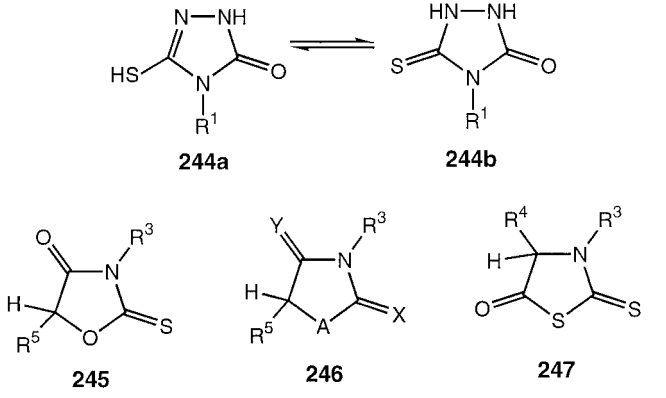


SCHEME 83

6. *Hydroxymercaptoazoles*

The oxo–thione form **241** is taken for 2-mercapto-4-hydroxyimidazoles (Scheme 83) [76AHC(S1), p. 463]. These tautomeric equilibria were clarified by the consideration of models in which some tautomeric forms were blocked. Thus, for S-alkylated 5,5-diphenyl **242** or 5-spirocyclohexyl **243** derivatives, oxo–thiol forms are the major tautomers [73T3565; 76AHC(S1), p. 463].

No definite choice between the two tautomeric forms was made in early studies of 5-mercapto-1,3,4-triazolin-2-one **244** (Scheme 84) [76AHC(S1), p. 464]. The oxo–thione form **245,** similar to **241,** was attributed to 2-mercapto-4-hydroxyoxazole and its derivatives based on IR-spectro-



SCHEME 84

scopic studies [72SA(A)855; 76AHC(S1), p. 461]. Similar tautomeric forms were also assigned to analogous derivatives of thiazole **246** (A = X = S; Y = O) [76AHC(S1), p. 462; 85JPR251], **247** [76AHC(S1), p. 463], and selenazole **246** (A = Se; X = S; Y = O) [76AHC(S1), p. 463; 96CHEC-II(3)493].

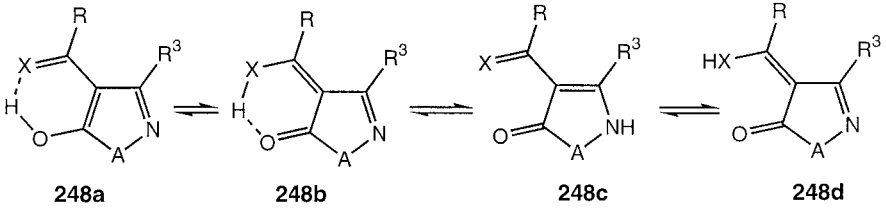
E. Azoles with Chelated Potential Tautomeric Groups

1. *Hydroxycarbonyl (Thiocarbonyl) Compounds*

In nonpolar solvents, 4-acyl-5-pyrazolones **248** (A = NR^1, X = O) exist as the chelated hydroxy tautomers **248a** (Scheme 85) [75JHC85; 76AHC(S1), p.334; 77ZOR1710, 77ZOR1750; 84SA(A)397; 94CPL559; 99H(50)799]. In the solid, both enol and keto forms of **248** could be prepared separately depending on the nature of the substituent R [99H(50)799] as well as on the solvent used. Thus, enol tautomers of **248** (A = NMe, NPh; X = O) were obtained from *n*-hexane, while growing the crystals from MeOH gave keto tautomers [85AJC401; 95AX(C)1310]. Tautomers **248c** may contribute to equilibrium mixtures of tautomers of **248** in solution and in the solid state (77ZOR1750; 94CPL559). For the isoxazolone derivatives **248** (A = O) the main components of the tautomeric equilibrium are represented by the tautomers **248a** and **248b** [72UK877; 75JHC85; 76AHC(S1), p. 304; 95ZN(B)37; 96MI653]. However, in the solid, the nonchelated NH–oxo form **248c** (R = R^3 = Ph) has been demonstrated using X-ray study [95ZN(B)37]. A certain amount of form **248c** is also found in methanol solution (96MI653).

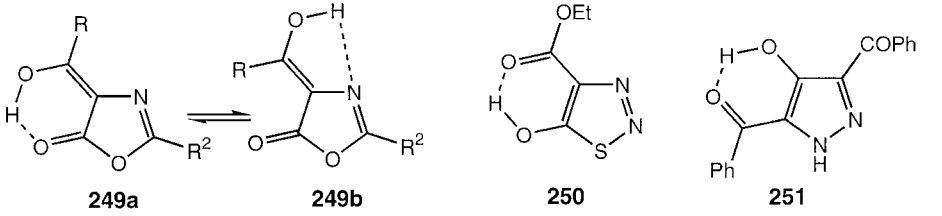
Chelated oxo structures were assigned to 5-hydroxy-4-acyl-1,3-oxazoles on the basis of their ^{1}H NMR spectra, the preference being given to the conformer **249a** with a six-membered chelate ring (Scheme 86) (75BSB845).

The chelated tautomeric forms shown are prepared for 4-ethoxycarbonyl-1,2,3-thiadiazole-5-one **250** and 3,5-dibenzoyl-4-hydroxypyrazole **251** [76AHC(S1), pp. 359, 384].



248a **248b** **248c** **248d**

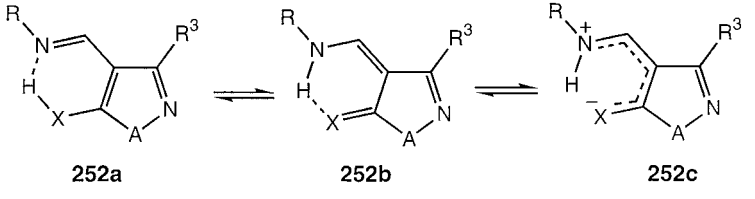
Scheme 85



SCHEME 86

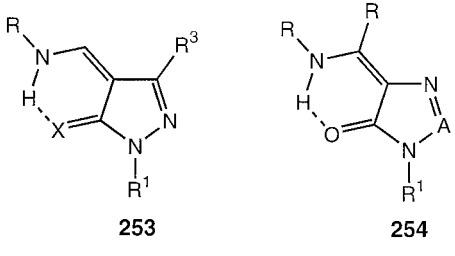
2. *Hydroxy- and Mercaptoaldiminoazoles*

Apart from a section in the monograph [76AHC(S1), pp. 307, 336], several concise reviews were devoted to the tautomerism of compounds of type **252** (Scheme 87) [82MI663; 92KGS5, 92MI321; 93CCR1].



SCHEME 87

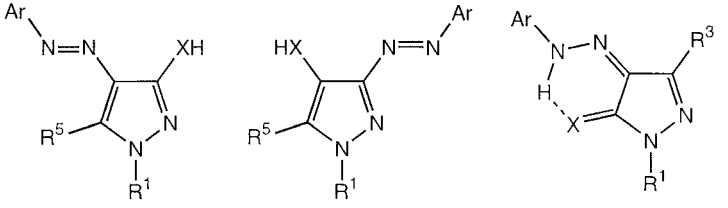
For the pyrazoles (A = NR^1, X = O, S; R, R^1 = H, Alk, Ar, Het; R^3 = Alk, Ar) the major tautomer is the aminomethylene structure **252b** [74ZOR2210; 75BSB741, 75ZOR1734; 78JPR17, 78JPR508, 78JPR521, 78ZSK620, 78M1093; 94ZOB657], which is stabilized by resonance with the zwitterionic structure **252c** [74ZOR2210; 78JPR508, 78JPR521, 78M1093; 92MI321, 94ZOB657]. This conclusion has been supported by X-ray structural determinations of **253** (X = O, R = 8-quinolyl, R^1 = Ph, R^3 = Me) (99UP1) and **253** (X = S, R = *c*-C_6H_{11}, R^1 = *i*-Pr, R^3 = Me) (89MI1).



Aminomethylene tautomers are also favored for the 5-imidazolones **254** (A = CR^2) (78KGS1677) and 1,2,3-triazolones **254** (A = N) (84JHC1603).

3. *Arylazo Derivatives of Hydroxy- and Mercaptoazoles*

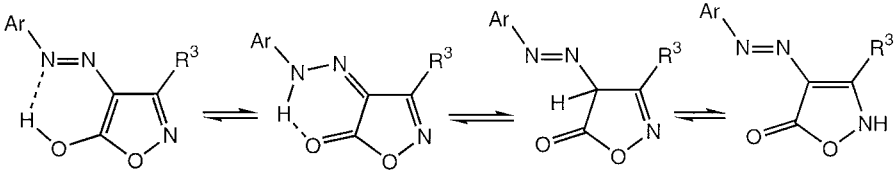
Little is known about possible tautomerism of 3-hydroxy-4-azopyrazoles **255** (X = O) and 4-hydroxy-3-azopyrazoles **256** (X = O), which are usually considered to be hydroxy compounds [76AHC(S1), pp. 346, 359].



255 **256** **257**

By contrast, oxo (X = O) or thione (X = S) forms are the only tautomers found for 5-hydroxy(mercapto)-4-arylazopyrazoles **257** in solution [72UK877; 76AHC(S1), p. 336; 84BSF(2)164, 84CHEC-I(5)167; 90JCS(P2)203; 91JHC641] or in the crystal [90JCS(P2)203] regardless of the type of substitution (R^1, R^3, Ar).

A similar type oxo–hydrazonic tautomer **258b** is most probably the favored form for 5-hydroxy-4-arylazoisoxazoles [72UK877; 80JHC897], although coexistence with other tautomers cannot be ruled out (Scheme 88).

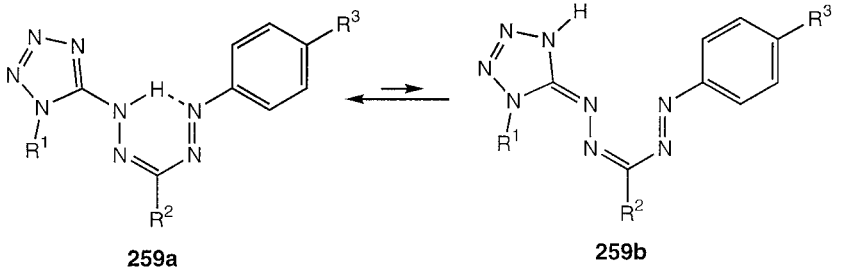


258a **258b** **258c** **258d**

SCHEME 88

4. *Azolyl- and Benzazolylformazanes*

Recent years have seen significant progress in our understanding of the tautomerism of azolyl- and benzazolylformazanes [75UK1052; 76AHC(S1), p. 446; 92MI144; 93K113]. In the tautomeric equilibrium of tetrazolylformazanes **259** the major form is the amino tautomer **259a** (Scheme 89)



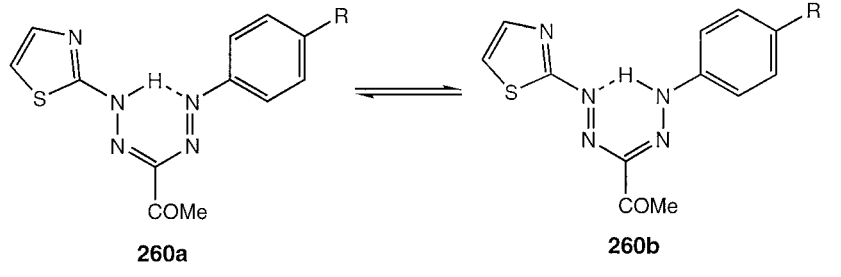
SCHEME 89

(79ZOR2207). By the use of IR spectroscopy the content of **259a** was found to be 86% in chloroform and 69% in CCl_4.

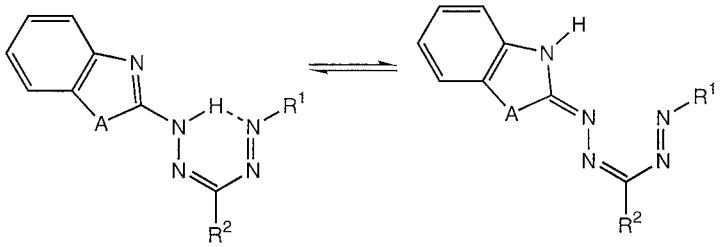
The position of the tautomeric equilibrium in thiazolylformazanes **260** only slightly depends on the solvent used; however, the nature of the substituent R in the aromatic ring plays an essential role (Scheme 90). Thus, it was shown that the amount of the tautomer **260b** significantly increases with increasing electron-accepting character of R up to 70% for R = NO_2 [86ZOB2393].

For 2-benzazolylformazanes **261,** the major tautomer is determined by the basicity of the benzazole moieties (Scheme 91) (75UK1052; 92MI144).

Benzoxazolyl (A = O) and benzothiazolyl (A = S) formazanes **261,** with substituents of relatively low basicity, exist as the amino tautomers **261a** (75UK1052; 92MI144) as shown by X-ray structural determinations of **261** (A = S; R^1 = C_6H_4OMe-*p;* R^2 = Ph) (83ZOR2615), **261** (A = S; R^1 = R^2 = Ph) (90K1133; 91KGS1268), **261** (A = S; R^1 = 1-naphthyl; R^2 = Ph) (90K1133), and **261** (A = S; R^1 = C_6H_4Me-*o;* R^2 = Me) (93K113). The amino form **261a** was also proven for benzothiazolylformazanes (A = S; R^1 = C_6H_4R-*p;* R = H, Me, OMe, NMe_2, Cl, Br, COOH; R^2 = Ph) in the gas phase (83ZOR2615).



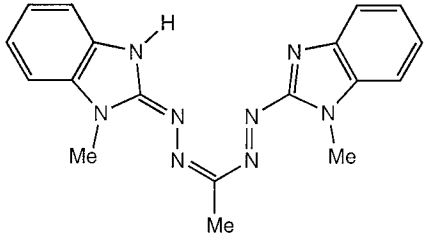
SCHEME 90



261a **261b**

SCHEME 91

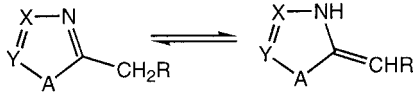
The more basic benzimidazolylformazanes **261** (A = NR^3; R^1, R^2 = Alk, Ar, Het; R^3 = Alk) prefer the imino tautomeric form **261b** [73KGS699; 75UK1052; 92MI144]. 1,5-Di-(1′-methylbenzimidazolyl-2)-3-methylformazan exists as amino–imino tautomer **262** [90ZSK117].



262

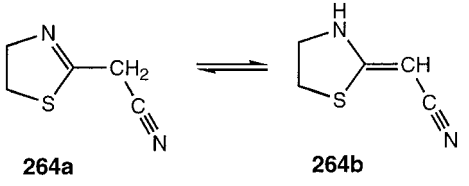
F. OTHER AZOLE-CONTAINING SYSTEMS

Relatively little is known about the methyl–methylene tautomerism of azoles **263** (Scheme 92) [76AHC(S1), p. 491]. In compounds with 1,3-heteroatoms (A = NR, O, S; X, Y = CR^1, N; R^1 = H, Alk, Ar, AlkAr), the mobility of the proton of the CH_2R group increases substantially with increase in the electron-withdrawing ability of the substituent R (see, for example, R = CN [78CR(C)385], NO_2 [76AHC(S1), p. 492], $COCH_3$ or $COOCH_3$ [76AHC(S1), p. 492; 78CR(C)385]). An equilibrium in the thiazoline **264** can serve as another example of this type of tautomerism (Scheme 93) (92UKZ935).



263a **263b**

SCHEME 92

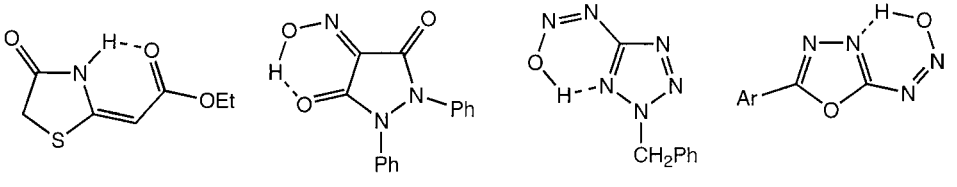


264a **264b**

SCHEME 93

Stabilization of the methylene tautomer may be attained also through the formation of a conjugated chelated structure, as is the case of **265** [76AHC(S1), p. 493].

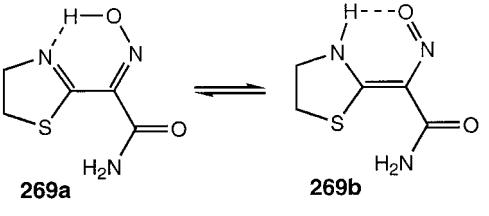
Nitroso–oxime tautomerism was reported to occur in compounds **266–268** [76AHC(S1), pp. 436, 443, 452].



265 **266** **267** **268**

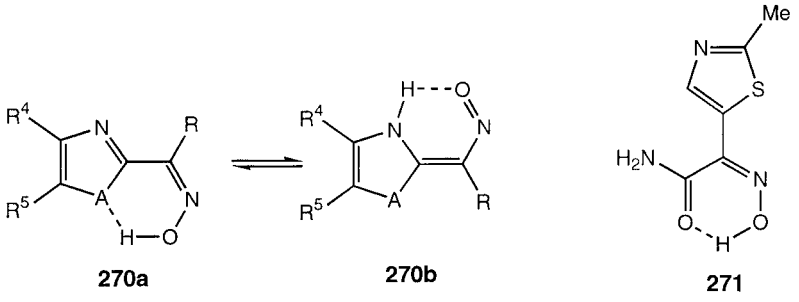
A recently documented example of the tautomerism of this type is the equilibrium **269** (Scheme 94) (95ZOB1031). In DMSO, thiazolineisonitrosomethamide contains at equilibrium up to 20% of the nitroso tautomer **269b** (95ZOB1031; 98MI1).

Similar type of tautomerism is known also for the heteroaromatic azoles **270** and **271** (Scheme 95) (97ZOB1572; 98MI1). X-Ray structural determinations indicate the oxime tautomeric forms for the compounds **270** [(A = S; R = $CONH_2$; R^4 = Me; R^5 = H) (95ZOB1031; 96ZOB1501; 98ZNK246), (A = S; R = CN; R^4 = Me; R^5 = H) (96ZOB989), (A = S; R = CN; R^4 = R^5 = C_6H_4-cyclo) (97ZOB1572), (A = Se; R = CN; R^4 = Me; R^5 = H) (96ZOB1493)] and **271** (96ZOB1364) in the solid state.



269a **269b**

SCHEME 94



SCHEME 95

G. CONCLUSION

While significant amounts of experimental data are available on the side-chain tautomerism of the functionalized azoles, most are of qualitative character and not fully systematic. No accurate structural correlations which would allow reliable predictions of the energy preferences of a specific tautomer or the state of a tautomeric equilibrium at given conditions have been developed. Nevertheless, trends can be discerned, some of which have previously been formulated [76AHC(S1), pp. 386–391, 443–446]. More recent studies discussed in this section have confirmed the validity of the following:

1. Aminoazoles mostly exist as such with no evidence of amino–imino tautomerism. However, imino tautomers of the aminoazoles can be stabilized either by an electron-withdrawing substituent attached to the amino group or by azole ring substituents, enabling the formation of a chelate rings involving the substituted imino group.
2. For hydroxy- and mercaptoazoles, hydroxy–oxo and thiol–thione tautomeric equilibria depend strongly on the orientation of the substituents and heteroatoms. Most 2- and 5-hydroxy(mercapto)azoles exist mainly as oxo (thione) tautomers, but the corresponding 3- and 4-isomers often prefer the hydroxy (mercapto) forms.
3. Occurrence of the methyl–methylene tautomerism in azoles needs a strong electron-withdrawing substituent attached to the methyl group.
4. The nature and position of the cyclic heteroatoms within the five-membered rings of azoles can affect the positions of the prototropic tautomeric eqilibria, particularly of hydroxy and mercapto derivatives.

III. Ring-Chain Tautomerism

In recent years significant progress has been achieved in the study of the ring-chain tautomerism of five-membered nitrogen-containing heterocycles [78MI2; 85MI1; 88KGS3; 95AHC(64)251, 95ZOB705; 96AHC(66)1]. Infor-

mation on earlier studies of tautomeric equilibria of this type was summarized in earlier reviews [63AHC(1)167, 63CRV461; 73UK1060; 74UK1417] and monographs [76AHC(S1), p. 498; 78M12].

A. N,N-Containing Heterocycles

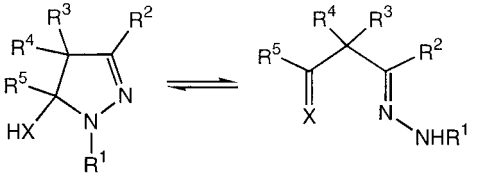
1. *Pyrazolines and Pyrazolidines*

Pyrazolines **272** exhibit diverse ring-chain tautomeric rearrangements **272** to **273**–**275** (Scheme 96). These involve equilibria with hydrazones **273** [88KGS3; 95AHC(64)251, pp. 294, 295; 95ZOB705; 96AHC(66)1, pp. 38, 39, 42; 97KGS1228, 97ZOR418], bis-hydrazones **274** [88KGS3; 95ZOB705; 96AHC(66)1, pp. 38, 39, 42], and hydrazone oximes **275** [96AHC(66)1, pp. 49–50].

Usually, the cyclic isomers **272** are preferred in the solid state. X-Ray structural evidence was obtained for compound **272** [R^1 = COPh, R^2 = Me, R^3 = R^4 = H, R^5 = CF_3; X = O (92KK1184)]. In solution, the cyclic and ring-opened isomers are found in equilibria in ratios depending on polarity of the solvent and structural factors (see 88KGS3; 95ZOB705; 96AHC(66)1 for reviews).

In recent years special attention has been given to ring-chain tautomerism of pyrazolines derived from 1,3-diketones with perfluoroalkyl groups (97ZOR418) **272** (X = O; R^1 = COC_6H_4Y; Y = H, Me, OMe, Br, NO_2; R^2 = Me, CF_3; R^3 = R^4 = H; R^5 = *t*-C_4H_9, C_3F_7, C_8F_{17}). In solution ($CDCl_3$, DMSO-d_6, pyridine-d_5), the equilibrium content of the ring-opened form **273** increases with increase in solvent polarity and electron-donor ability of the aryl substituent R^1. In the solid, the cyclic tautomers are preferred as proven by IR spectroscopy (97ZOR418).

The tautomerism of 3-amino(hydrazino)pyrazolidines **276** [88KGS3; 96AHC(66)1, pp. 36, 37] and 3-hydroxypyrazolidines **277** [95AHC(64)251,

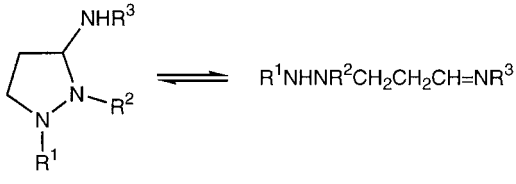


272 **273-275**

273: X = O; **274**: X = $NNHR^1$;
275: X = NOH

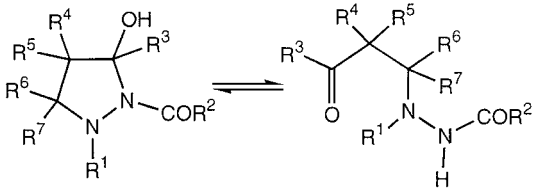
R^1 = H, Alk, Ar, C(O)Alk, C(O)Ar, C(S)Ar
R^2 = H, Alk, COOMe; R^3, R^4 = H, Alk
R^5 = Alk, Ar, OMe

Scheme 96



276a **276b**

R^1 = *i*-Pr, Ph, $PhCH_2$, COMe; R^2 = *i*-Pr, Ph;
R^3 = C_6H_4X-*p*, NR^4R^5; R^4R^5 = H, Alk, Ph, C_6H_4X-*p*

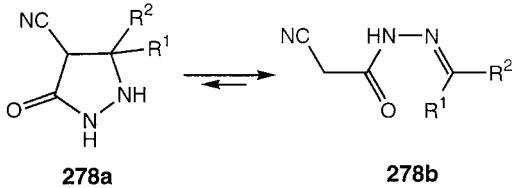


277a **277b**

SCHEME 97

p. 293] has been extensively studied (Scheme 97). According to mass-spectroscopic evidence, in the gas phase the compounds **276** exist as the ring-opened isomers **276b.** As ^{1}H NMR study shows, this is also true for these hydrazino derivatives in solution, whereas the hydroxy derivatives **277** are stable in the cyclic form **277a.**

The position of the tautomeric equilibria in the gas phase and solutions of 4-cyano-5-pyrazolidones **278** is unclear [95KGS1525; 96AHC(66)1, p. 53]. With the exception of **278** (R^2 = 4-$O_2NC_6H_4$), it was assumed that all these compounds exist as the ring-opened tautomers **278b** (Scheme 98). However, in a review [96AHC(66)1, p. 53] with the reference to (88AKZ385) the cyclic tautomers **278a** were treated as the dominant forms.



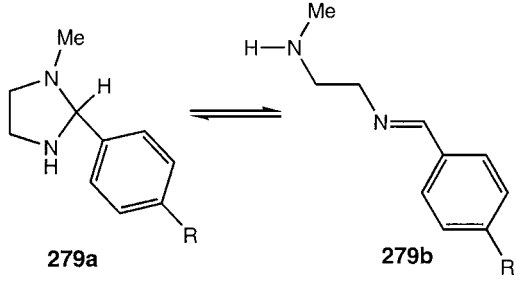
278a **278b**

SCHEME 98

2. *Imidazolines*

The ring-chain tautomerism of the imidazolidines **279** (80H1313) is of interest (Scheme 99). The isomer ratio is determined by the nature of the substituents and is hardly affected by the polarity of the solvent (CCl_4, DMSO).

The only example of ring-chain tautomerism of imidazoles is 1-hydroxy-Δ^3-imidazoline-3-oxide (69MI86; 78MI2, pp. 155, 182).



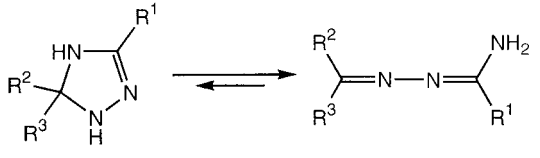
279a **279b**

R = H, NMe_2, NO_2, NHAc, NHCOOPr-*i*

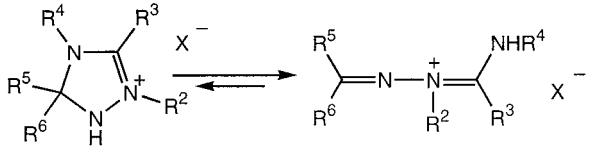
SCHEME 99

3. *Triazolines and Triazolidines*

The predominant form of the compounds **280** is their amidrazonic tautomer **280b** (Scheme 100) (88KGS3). On protonation of **280,** or as their quaternary salts **281** (R^1 = Alk), for the compound with R^2 = Ph, the con-

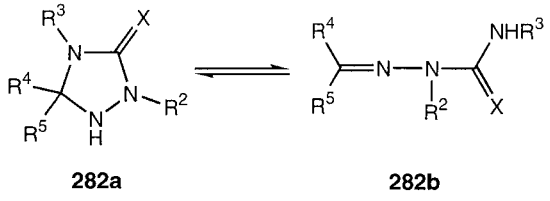


280a **280b**



281a **281b**

SCHEME 100



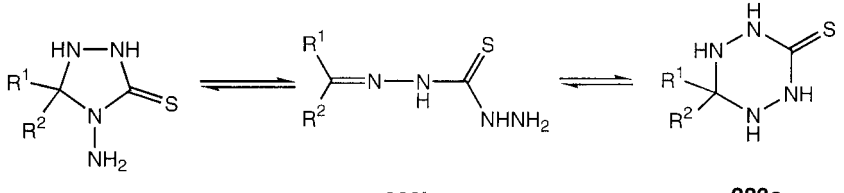
282a **282b**

SCHEME 101

tent of the cyclic form is less than 10% (88KGS3). The reasons for the energetical preference of the acyclic tautomers **281b** have been analyzed (Scheme 100) [96AHC(66)1, pp. 27, 51].

Similar behavior was also observed for analogous 3-oxopyrazolidines **282** (X = O) and pyrazoline-3-thiones **282** (X = S) (Scheme 101).

Ring-chain tautomerism of derivatives of 1,3,4-triazolidines **283** involves the equilibrium of three isomeric forms (Scheme 102) [90TL3927; 96AHC(66)1, p. 33]. In DMSO solution, the predominant form (about 70%)is **283c,** the content of **283a** and **283b** varied between 13–25% and 5–17% respectively.



283a **283b** **283c**

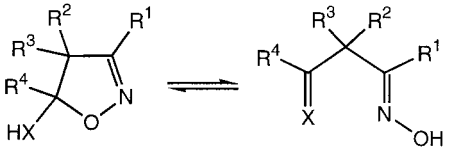
SCHEME 102

B. N,O-CONTAINING HETEROCYCLES

1. *Isoxazolines and Isoxazolidines*

For the isoxazolines **284** substituted at position 3, ring-chain tautomerism is depicted by the equilibrium **284** and **285**–**287** (Scheme 103). In general the cyclic tautomers **284** are strongly preferred. The ring-opened forms exist in equilibrium with **284** in rare cases [95ZOB705; 96AHC(66)1, p. 21]. The equilibrium of the oxazolidinones **288** [78MI1, p. 107] is affected by the nature of the solvent.

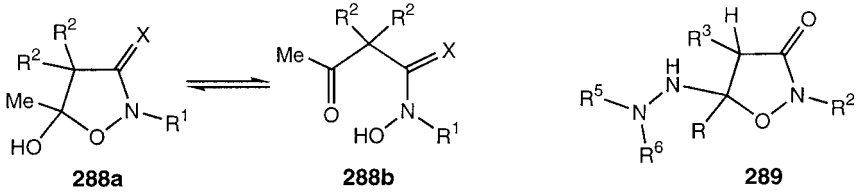
The tautomerism of the hydrazino derivatives **289** has been discussed in (95ZOB705).



284 **285-287**

285: X = O; **286**: X = NNHR;
287: X = NOH

R^2 = Me, CH_2Ph, $COCH_2Ph$;
R^3 = H, Me, CH_2Ph; R^4 = Ph, CH_2Ph



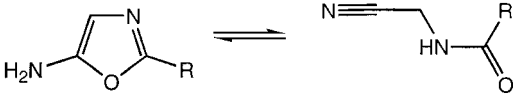
288a **288b** **289**

X = H_2, O; R^1, R^2 = H, Alk

SCHEME 103

2. *Oxazoles, Oxazolines, and Oxazolidines*

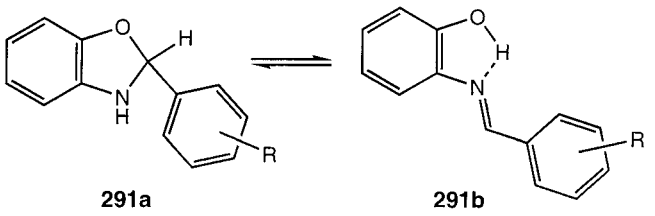
The only example of ring-chain tautomerism of oxazoles **290** known so far was described in 84CHEC-I(6)177 (Scheme 104).



290a **290b**

SCHEME 104

2,3-Dihydro-2-arylbenzoxazoles **291** exist in the solid state and in solution in acyclic forms **291b** (Scheme 105) [59JA1523; 84CHEC-I(6)177, p. 186; 90T6545; 96AHC(66)1, p. 8].

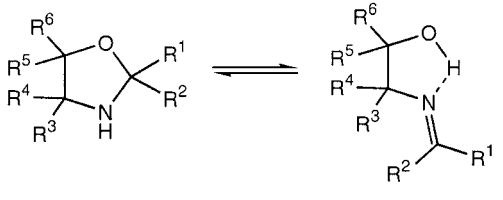


291a **291b**

R = H, Me, OH, OMe, NMe_2, NO_2, Cl

SCHEME 105

The ring-chain tautomerism of oxazolidines **292** is much studied (Scheme 106) [71T4407; 78MI2, p. 136; 84CHEC-I(6)177, p. 187; 95AHC(64)251, p. 270, 95ZOB705; 96AHC(66)1, p. 3]. Thermodynamic parameters were determined [92JOC2446; 96AHC(66)1, p. 5] and the substantial influence of the origin of the R^2 substituent proven. Destabilization of the minor cyclic form by substitution was observed in the order Et < *i*-Pr < *t*-Bu. Electron-releasing substituents X, such as X = 4-NMe_2, ($R^1 = C_6H_4X$) also shift the equilibrium toward the acyclic form ($K_T \approx 0$, $CDCl_3$, 35°C) (91ZPK1052), whereas electron-withdrawing substituents increase the equilibrium content of the cyclic tautomer, e.g., when X = 4-NO_2 ($K_T = 0.169$).



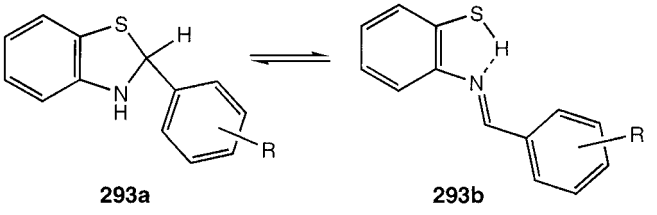
292a **292b**

SCHEME 106

C. N,S-CONTAINING HETEROCYCLES

1. *Thiazolines and Thiazolidines*

Ring-chain tautomerism of these compounds is exemplified by 2-aryl-2,3-dihydrobenzothiazolines **293** (Scheme 107) [68JHC509; 88TL5427; 90T6545; 93CCR1; 96AHC(66)1, p. 43] and analogous 2-heteroaryl derivatives (87RRC151). The stable form of these compounds in solution is the cyclic structure **293a.** The factors that favor the acyclic tautomer, in particular complexation with metal salts, are considered in Section V and in 87RRC151.

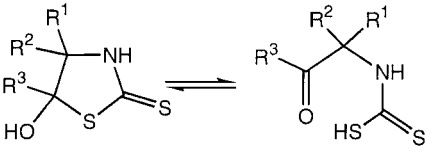


293a **293b**

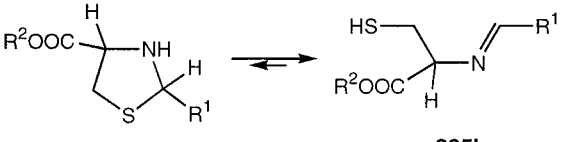
R = H, 2-OH, 4-NMe_2, 5-Br

SCHEME 107

The tautomerism of thiazolidines [78MI2, p. 130; 95ZOB705; 96AHC(66) 1, p. 43] is more studied. 5-Hydroxy-2-thiazolidinethiones **294** have the cyclic structure **294a** both in the crystal and solution (Scheme 108) [78MI1, p. 130]. However, for the compound **294** with a bulky *tert*-butyl group (R^2 = *t*-Bu), the ring-opened form **294b** was observed in equilibrium with **294a.** An equilibrium of the cyclic and ring-opened forms exists also in solutions of **295** [96AHC(66)1, p. 43].



294a **294b**

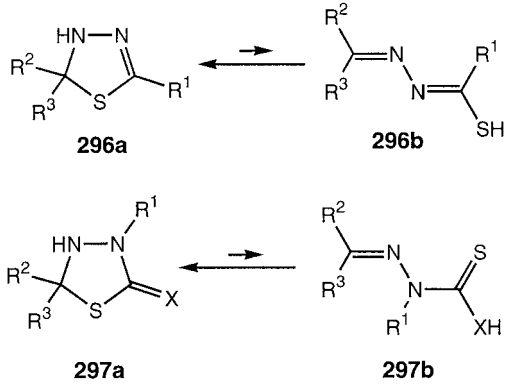


295a **295b**

SCHEME 108

2. *Thiadiazolines and Thiadiazolidines*

Ring-chain tautomerism was studied for 1,3,4-thiadiazolines **296** and 1,3,4-thiadiazolidines **297** (Scheme 109) [78MI2, p. 159; 84CHEC-I(6)545, p. 557; 88KGS3; 95ZOB705; 96AHC(66)1, pp. 44, 46, 52]. In all these cases the equilibria are shifted to the cyclic structures. Quantitative aspects of these equilibria have been discussed elsewhere [96AHC(66)1, pp. 44–46].



SCHEME 109

IV. Valence Tautomerism

A. Scope of Valence Tautomerism

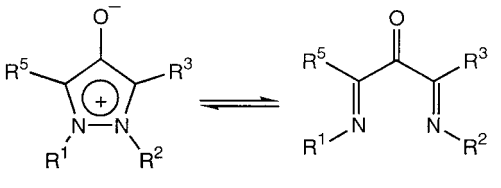
Various isomerization reactions (both degenerate and nondegenerate) are defined as the reversible rupture and formation of bonds in a molecule occuring without transfer of any group. They constitute valence tautomeric systems provided their thermodynamic and activation parameters fit the requirements of the Eqs. (1) and (2). Valence tautomerism may be classified by the types of bond making and bond breaking as π-valence, σ,π-valence, and σ,σ-valence tautomerism (88MI1). The most frequently occurring examples of valence tautomerism of this style belongs to the second group. These involve both redistribution of the π-bonds and also changes in the framework of σ-bonds when passing from one tautomer to another. All the tautomeric transformations considered below belong to these σ,π-valence tautomeric interconversions.

B. Valence Tautomerism of Azoles

Examples of this type of valence tautomerism are few in number [76AHC(S1), p. 498; 78MI1, p. 9; 96CHEC-II(4), pp. 1, 165, 379, 96KGS1581].

1. *Pyrazoles*

The possibility of the equilibrium **298a/298b** for sydnones was considered [76AHC(S1), p. 498], but not yet firmly established (Scheme 110).



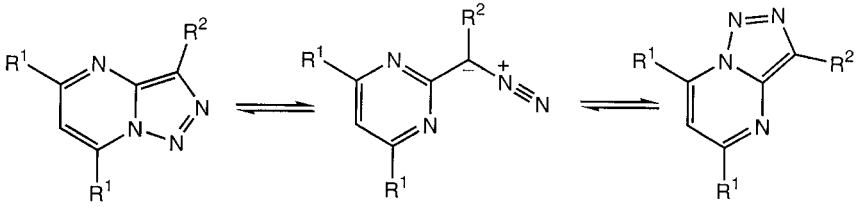
298a **298b**

SCHEME 110

2. *Triazoles*

Simple examples of diazoalkylideneamine–1,2,3-triazole equilibria have been demonstrated for a series of 1,2,3-triazolo[1,5-*a*]pyrimidines by variable-temperature ^{1}H NMR [74JCS(CC)671]. Tautomers **A, B,** and **C** interconvert rapidly at elevated temperatures; the energy barrier for these ring-opening–ring closure processes was found to be $\Delta G^{\neq} = 76$ kJ mol^{-1} (for R^1 = H, Me; R^2 = $CONH_2$) (Scheme 111).

An equilibrium involving reversible dissociation of the N-N bond in *N*-nitrobenzotriazole **299a** has not been directly registered, although occurrence of the ring-opened form **299b** was inferred on the basis of isolation of its derivative **300** (Scheme 112) [96CHEC-II(4)1].

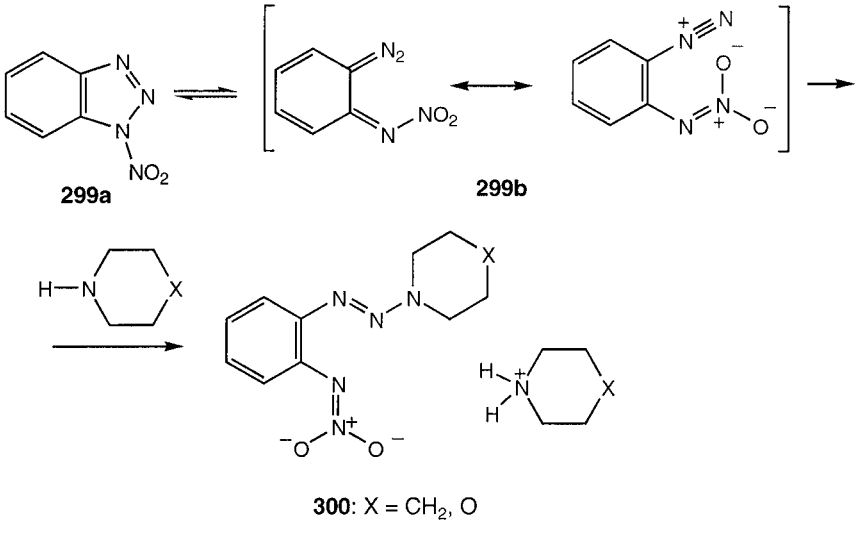


A **B** **C**

SCHEME 111

3. *Tetrazoles*

Valence tautomerism of heterocyclic systems containing tetrazole rings has received much attention [76AHC(S1), p. 498; 84CHEC-I(5)791; 96CHEC-II(4)621]. The latest contributions to this area are considered in Section IV,C, which is concerned with the topic of azido–tetrazole tautomerism.

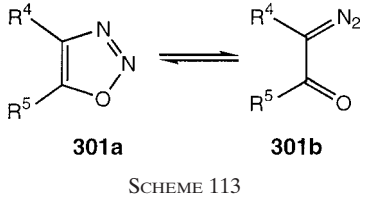


SCHEME 112

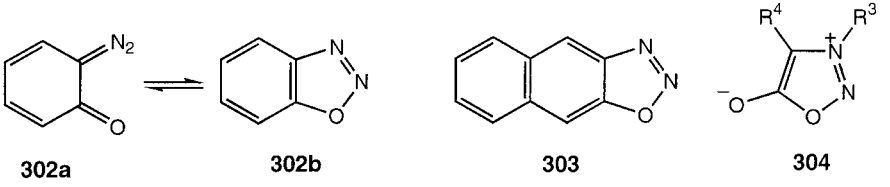
4. *Oxadiazoles*

Cleavage of the N-O bond in the five-membered rings provides for a possibility of the equilibrium **301a** ⇌ **301b** (Scheme 113) [96CHEC-II(4)165]. In $CDCl_3$ solution, the only observable isomer is the diazoketone **301b** [96CHEC-II(4)165].

6-Diazo-2,4-cyclohexadienone **302a** exists in equilibrium with 1,2,3-benzooxadiazole **302b** both in the gas phase and in solution, as demonstrated by UV/Vis- and IR-spectroscopic studies (Scheme 114) [84AG(E)509; 91JST135]. The position of the equilibrium depends strongly on the nature of substituents in the benzene ring and the polarity of solvent (non-polar solvents favor the ring-closed form **302b**). Naphtho-annelated 1,2,3-oxadiazoles **303** (94CB551) and the sydnones **304** (96KGS1581) prefer ring-closed structures.

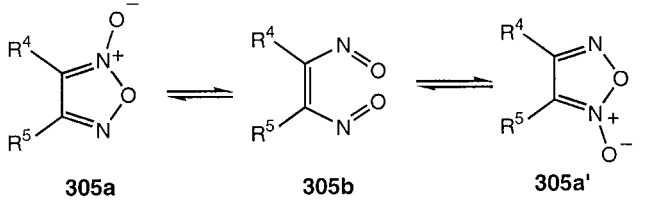


SCHEME 113



SCHEME 114

For 1,2,5-oxadiazole-2(5)*N*-oxides and their benzoannelated derivatives, a tautomeric equilibrium is conceivable in which two cyclic *N*-oxides **305a** and **305a′** participate with a ring-opened **305b:** in fact, the dinitroso structure is of much higher energy but is implicated in the equilibrium between **305a** and **305a′** (Scheme 115) [66UK1324; 78MI2, p. 10; 96CHEC-II(4)229].

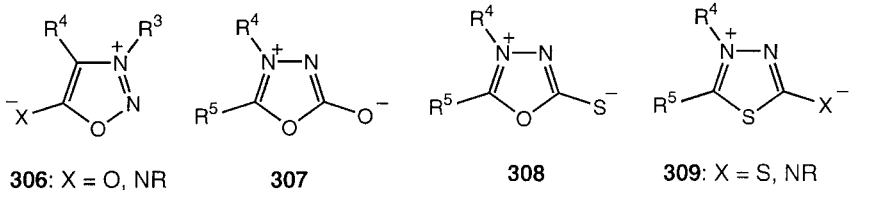


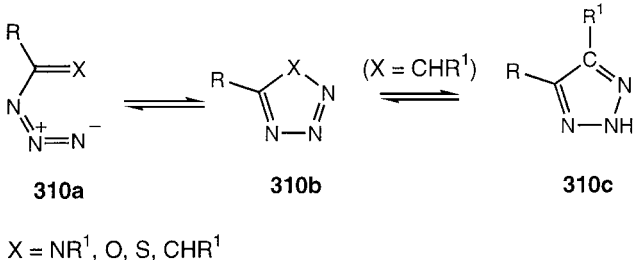
R^4, R^5 = alkyl, *cyclo*-C_4H_4

SCHEME 115

1,2-Dinitrosobenzene **305b** [$R^4R^5 = (CH)_4$] has been trapped in an argon matrix at 14 K and characterized by IR and UV spectroscopy [96CHEC-II(4)229].

Multinuclear ^1H, ^{13}C, ^{14}N, ^{15}N, and ^{17}O NMR data demonstrate that valence tautomerism does not take place in solution for diverse series of sydnones (**306**), isosydnones (**307**,**308**), and isothiosydnones (**309**) (96KGS1581). Only the mesomeric zwitterionic forms **306–309** were observed, in agreement with *ab initio* calculations.





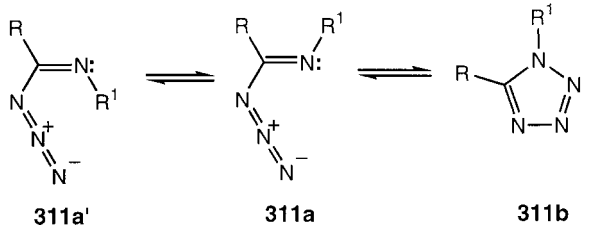
SCHEME 116

C. AZIDO–TETRAZOLE TAUTOMERISM

The general scheme for this type of tautomeric reaction is **310a** ⇌ **310b.** When X = O, the azido form **310a** dominates and no oxatriazole tautomer is detected (Scheme 116) [84CHEC-I(6)579]. With X = S, the situation is the reverse: the thiatriazole form **310b** is strongly energetically preferred [96CHEC-II(4)691]. The same applies for X = CHR^1, i.e., the vinyl azide – 1,2,3-triazole transformation also shows significant energy preference of the cyclic form **310c** (74JOC1778; 78JA3668).

The smallest energy gap between the interconverting isomers **310a** and **310b** is for azidoazomethine/tetrazole species (X = NR^1). For this reason, and because the rearrangement **310a** ⇌ **310b** is a main synthetic approach to tetrazoles, it has received special attention and was fully reviewed [71MI57; 73CIL371, 73S123; 75UK1028; 77AHC(21)323; 78AHC(22)183; 84CHEC-I(5)791; 96CHEC-II(4)621]. The cyclization of the azidoazomethine tautomer **310a** (X = NR^1) requires a *cis*-orientation of the imino lone pair and the azido group [77AHC(21)323; 80JCS(P2)535; 84JCS(CC)913; 96CHEC-II(4)621] (see equilibrium **311a′** ⇌ **311a** ⇌ **311b**, Scheme 117).

The participation of the lone-pair orbital in the cyclization process allows its classification as a so-called pseudopericyclic reaction (76JA4325; 97JA4509), which is a subset of a general type of pericyclic reactions



SCHEME 117

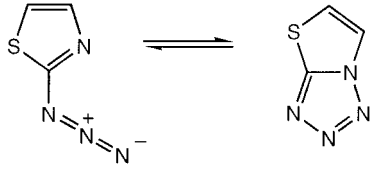
with no cyclic orbital overlap. Formally the transformation may also be described as an electrocyclic (71BSF1925) or a 1,5-dipolar cyclization (70CB1900). Detailed mechanisms for this type of interconversion have been studied theoretically using *ab initio* calculations which employ an STO-3G basis set (76JA1685). For the parent ($R = R^1 = H$) compound, the transition state resembles strongly the structure of the azide molecule, the NNN angle being the only geometric parameter varying substantially at this reaction step.

This conclusion was largely confirmed at the much higher (MP2/6-311G*) level of approximation for the case of interconversion of azido-azomethine and tetrazole forms of thiazole[3,2-*d*]tetrazole **312** (Scheme 118) (98JA4723).

The calculations (98JA4723) gave the value of the energy barrier as 88 kJ mol^{-1}, in good agreement with several experimental determinations [74JHC921, 74OMR485; 75TL1523; 78AHC(22)183]. Although kinetic studies of azide–tetrazole rearrangements are rather scarce, particular attention has been given to the influence of structural factors and media on the relative stabilities of the acyclic and cyclic isomers.

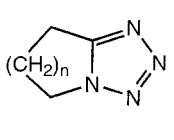
1. *Imidoyl Azides*

For the parent imidoyl azide **311** ($R = R^1 = H$), the equilibrium **311a** ⇌ **311b** is shifted totally to the right and the tetrazole **311b** is the sole form observed in the gas phase (74JSP423). Electron-withdrawing groups R, such as fluoroalkyl substituents (85IZV700), strongly favor the imidoyl azide form **311a.** Cyclization to **311b** is facilitated by electron-releasing groups R, but may be kinetically inhibited if the initial imidoyl azide is *trans*-**311a′** and cannot easily isomerize to **311a.** This is the case for a wide series of hydrazonoyl azides, **311** ($R^1 = NHR^2$), with electron-releasing substituents R [96CHEC-II(4)621]. When cis-configuration **311a** of an imidoyl azide is sterically enforced by inclusion of the substituents into a ring, tetrazoles, such as **313,** represent the only form observed in solution [75UK1028; 77AHC(21)323].

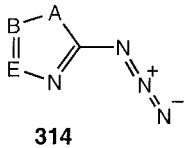


312a **312b**

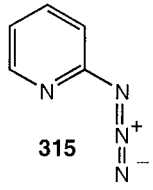
SCHEME 118



313



314



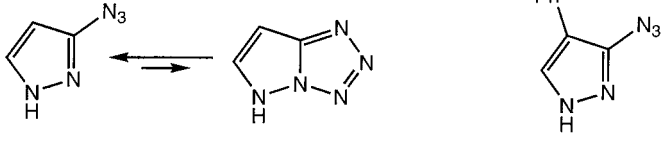
315

A favorable orientation of the lone pair at the imino nitrogen and the azido group is always achieved in heteroaromatic azides of azoles **314** and azines **315** [75ZOR1974; 77AHC(21)323, 77CJC1728; 78BSB189; 85AX(C)1199]. This factor lowers the energy barrier to the cyclization. On the other hand, an electron-withdrawing character of the heteroaromatic fragment decreases the relative stability of the tetrazole form and can thus furnish a delicate balance between the isomers. As a consequence the compounds of types **314** and **315** present the cases of the azido–tetrazole tautomerism most frequently met.

2. *Azidoazoles*

Real cases [i.e., those which satisfy the conditions of the Eqs. (1) and (2)] and potential cases of azido–tetrazole tautomerism have been fully studied for azidopyrazoles [75UK1028; 77AHC(21)323, 77MI545; 78AHC(22)183, 78BSB189], azidoimidazoles [75TL1523; 77JHC33, 77MI545; 79JHC685; 84CS(23)195], azidooxazoles (77CJC1728), azidoisoxazoles (77JHC1299), azidothiazoles (73CIL371, 73S123; 75BSB1189, 75UK1028; 76UK354; 77CJC1728, 77JHC1299; 96JHC747), azidotriazoles (77MI545), azidotetrazoles [77MI545; 86JCS(CC)959], and azidothiadiazoles [73CIL371; 77AHC (21)323, 77JHC1299].

In general, the equilibria are strongly shifted to the azido tautomer, which is considered to be a consequence of the relatively low aromaticity of the polyazapentalenic systems of the tetrazole tautomers [79JHC685; 86JCS(CC)959]. Thus, for the azidopyrazoles **316,** the tetrazole tautomers can hardly be detected: the equilibrium constant K_T = [**316a**]/[**316b**] is greater than 25 (Scheme 119) [73JOC2958; 74JCS(CC)411, 74JHC921;

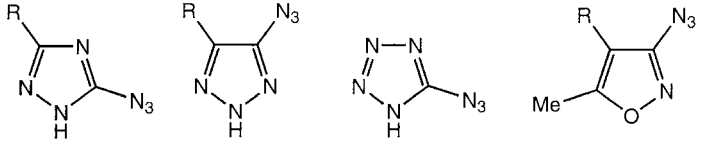


316a **316b** **317**

SCHEME 119

78BSB189]. However, deprotonation of **316a** leads to greater stabilization of the bicyclic anion of **316b** (74JHC921).

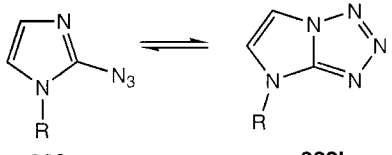
The azido-3(5)-phenyl-4-pyrazole isomer **317** is the sole form in the solid state by X-ray study (74CSC713). The azidoazole isomers also predominate in the case of 3(5)-azido-*s*-triazoles **318,** 4(5)-azido-*v*-triazoles **319,** azidotetrazole **320** [77MI545, 86JCS(CC)959], and azidoisoxazoles **321** (77CJC 1728, 77JHC1299).



318 **319** **320** **321**

In the case of azidoimidazoles, the position of the tautomeric equilibrium **322a** ⇌ **322b** is affected by the type of the substituent R and the solvent (Scheme 120) [75TL1523; 77AHC(21)323, 77JHC33; 96CHEC-II(3)77]. For compounds with strong electron-withdrawing groups R, an equilibrium is established in DMSO solution: the K_T (35°C) values were determined by ^{1}H NMR measurements to be 0.48 (COMe), 0.16 (CO_2Et), and 0.03 (CHO) (77JHC33) (Table IX). The less polar solvent $CDCl_3$ favors the azide form: $K_T = 0.1$ for **322** (R = COMe) (75TL1523).

The thiazole derivatives exist in either the open-chain **323a** or the cyclic **323b** form depending on the substitution in the ring and the solvent (Scheme 121). In the gas phase the azido form of **323** ($R^1 = R^2 = H$) was found by high-level (up to QCISD(T)/6-311++G**) *ab initio* calculations (98JA4723, 98JOC2354) to be the major species. In solution, the equilibrium is shifted toward the tetrazole form: as the polarity of the solvent increases, the values of K_T vary in the range 0.05–32 (75BSB1189, 75UK1028; 77CJC1728, 77JHC1299; 96JHC747). The trend of stabilization of the cyclic form in polar media is well reproduced by *ab initio* calculations accounting for solvation with the use of SCRF methods (98JA4723, 98JOC2354). In the solid state, the equilibrium **323a** ⇌ **323b** ($R^1 = R^2$) is fully shifted to



322a **322b**

SCHEME 120

TABLE IX

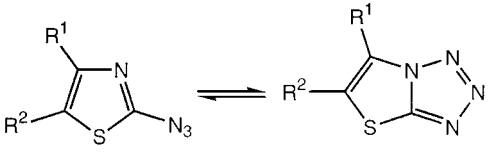
AZIDOAZOLE–TETRAZOLOAZOLE (A-T) TAUTOMERISM AS STUDIED BY ^{1}H-NMR SPECTROSCOPY

Compounds	Solvent[a]	Temperature (°C)	K_T = [A]/[T]	References
321	$CDCl_3$	28	≥50	77CJC1728, 77JHC1299
	DMSO-d_6	28	≥50	77CJC1728; 77JHC1299
322				
R = COH	DMSO-d_6	35	~0.03	77JHC33
R = COMe	DMSO-d_6	35	0.48	77JHC33
	$CDCl_3$	—	0.01	75TL1523
R = COOEt	DMSO-d_6	35	0.16	77JHC33
R = $COCH_2Cl$	DMSO-d_6	20	0.33	77JHC33
R = $COCHCl_2$	DMSO-d_6	20	0.24	77JHC33
323				
$R^1 = R^2 = H$	CCl_4	28	>25	75BSB1189
	TFA	28	>25	75BSB1189
	C_6D_6	28	15.5	75BSB1189
	$CDCl_3$	28	5.7	75BSB1189
	$CDCl_3$	30	5.7	77JHC1299
	$PhNO_2$	28	1.7	75BSB1189
	CD_3OD	28	1.2	75BSB1189
	Py	28	1.1	75BSB1189
	Acet	28	0.95	75BSB1189
	CD_3CN	28	1.0	75BSB1189
	DMSO-d_6	28	0.21	75BSB1189
	DMSO-d_6	30	0.21	77JHC1299
R^1 = Me, R^2 = H	CCl_4	28	5.0	75BSB1189
	TFA	28	10	75BSB1189
	C_6D_6	28	1.7	75BSB1189
	$CDCl_3$	28	0.85	75BSB1189
	$CDCl_3$	30	0.85	77JHC1299
	$PhNO_2$	28	0.22	75BSB1189
	CD_3OD	28	0.30	75BSB1189
	Py	28	0.30	75BSB1189
	Acet	28	0.17	75BSB1189
	CD_3CN	28	0.12	75BSB1189
	DMSO-d_6	28	0.03	75BSB1189
	DMSO-d_6	30	0.03	77JHC1299
R^1 = H, R^2 = Me	$CDCl_3$	28	0.68	77JHC1299
	DMSO-d_6	28	0.05	77JHC1299
$R^1 = R^2$ = Me	CCl_4	28	2.5	75BSB1189
	TFA	28	4.0	75BSB1189
	C_6D_6	28	1.1	75BSB1189
	$CDCl_3$	28	0.40	75BSB1189
	$CDCl_3$	30	0.40	77JHC1299
	$CDCl_3$	—	0.398	96JHC747

TABLE IX—*Continued*

Compounds	Solvent[a]	Temperature (°C)	K_T = [A]/[T]	References
323				
$R^1 = R^2 = Me$	$PhNO_2$	28	0.09	75BSB1189
	CD_3OD	28	0.18	75BSB1189
	Py	28	0.15	75BSB1189
	Acet	28	0.08	75BSB1189
	CD_3CN	28	0.07	75BSB1189
	DMSO-d_6	28	<0.04	75BSB1189
	DMSO-d_6	30	≤0.03	77JHC1299
$R^1 = H, R^2 = Cl$	$CDCl_3$	28	≥50	77JHC1299
	DMSO-d_6	28	1.60	77JHC1299
$R^1 = H, R^2 = Br$	$CDCl_3$	28	32	77JHC1299
	DMSO-d_6	28	1.60	77JHC1299
$R^1 = Ph, R^2 = H$	$CDCl_3$	20	16.5	77JHC1299
	DMSO-d_6	20	1.30	77JHC1299
$R^1 = p\text{-}NO_2C_6H_4$, $R^2 = H$	$CDCl_3$	28	≥20	77JHC1299
	DMSO-d_6	28	≥20	77JHC1299
324				
R = Me	C_6D_6	28	5.6	77JHC1299
	$CDCl_3$	28	3.9	77JHC1299
	CD_3OD	28	0.95	77JHC1299
	CD_3COCD_3	28	0.5	77JHC1299
	DMSO-d_6	28	0.15	77JHC1299
325				
R = H	$CDCl_3$	28	1.0	77JHC1299
	$CDCl_3$	—	1.000	96JHC747
	DMSO-d_6	28	0.08	77JHC1299
$R = NO_2$	$CDCl_3$	28	≥20	77JHC1299
	DMSO-d_6	28	≥20	77JHC1299
328				
$R = C_4H_9$	$CDCl_3$	—	2.951	96JHC747
330	$CDCl_6$	28	≥20	77JHC1299
	DMSO-d_6	28	≥20	77JHC1299

[a] Abbreviations: Acet, acetone; TFA, trifluoroacetic acid; Py, pyridine.



323a **323b**

SCHEME 121

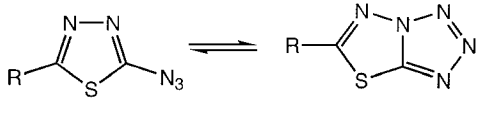
the thiazole[3,2-*d*]tetrazole form (75UK1028). Electron-donating groups R^1 and R^2 stabilize the tetrazole form (75BSB1189, 75UK1028; 77JHC33, 77JHC1299), whereas electron-accepting groups act in an opposite way (Table IX).

A similar behavior is also characteristic for the 2-azido-1,3,4-thiadiazole tautomeric system **324** and for 3-azidodihydropyrazoles containing (Scheme 122) electron-withdrawing groups (COR, Ts) at the pyrrole nitrogen [84CS(23)195]. Whereas the tetrazole tautomer **324b** is the sole species in the solid state, the position of the tautomeric equilibrium of **324** in solution depends strongly on the solvent used [77AHC(21)323, 77JHC1299]. Thus, the azide form **324a** usually prevails in nonpolar solvents (in C_6D_6 $K_T = 5.6$ and in $CDCl_3$ $K_T = 3.9$); however, polar solvents favor the tetrazole tautomer **324b** (in CD_3OD $K_T = 0.95$, in acetone-d_6 $K_T = 0.5$ and in DMSO-d_6 $K_T = 0.15$) (77JHC1299).

The role of annelation of arene rings was studied in most detail for the tautomeric equilibria in the series of 2-azidothiazole. In the solid state, 2-azidobenzothiazoles **325** exist in the form of tricyclic tetrazolo[1,5-*b*]benzothiazole tautomers **325b** [73UKZ215; 75UK1028; 77AHC(21)323], whereas azide forms dominate for the naphtho derivatives **326** and **327** (Scheme 123) (68DOK111; 75UK1028).

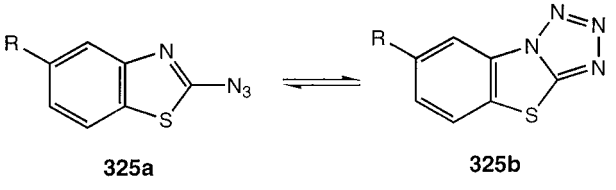
In solution ($CDCl_3$) both tautomers of **325** are found in the equilibrium [75UK1028; 77AHC(21)323; 96JHC747], $K_T \sim 1$ (R = H, 77JHC1299). This value of K_T indicates relative stabilization of the tetrazole tautomer as compared with the equilibrium **323a** ⇌ **323b** ($R^1 = R^2 = H$), where K_T = [**323a**]/[**323b**] = 5.7. Annelation to the benzene ring of **325** of an electron-accepting quinoline moiety shifts the equilibrium toward the azido form: K_T = [**328a**]/[**328b**] = 2.95 (R = C_4H_9, $CDCl_3$) (Scheme 124) (96JHC747).

Thus, the percentage of the azide tautomers increases from **323** ($R^1 = R^2 = CH_3$) (28.5%) to **325** (R = H) (50%) to **327** (R = C_4H_9) (75%) to **323** ($R^1 = R^2 = H$) (85%). The anion obtained from 2-azido-6*H*-thiazolo[5,4-*a*]acridin-11-one **328** (R = H) was found in the tetrazole form **328b** (96JHC747). Only azide isomers **329** and **330** exist in solutions of these benzimidazole and benzoxazole derivatives (75UK1028; 77JHC1299).

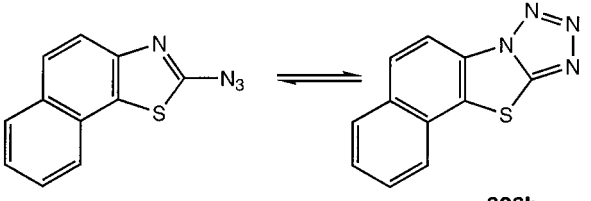


324a **324b**

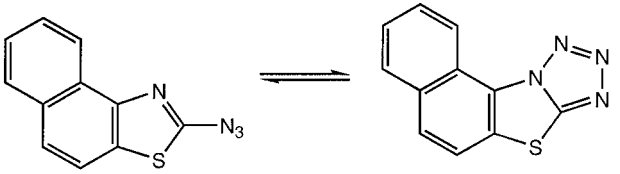
SCHEME 122



325a 325b

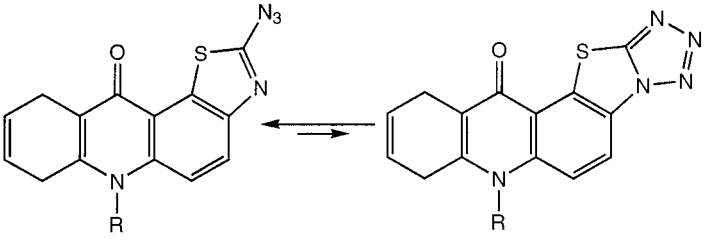


326a 326b



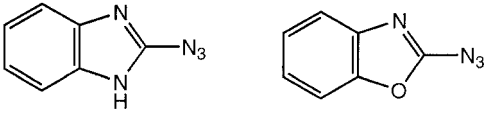
327a 327b

SCHEME 123

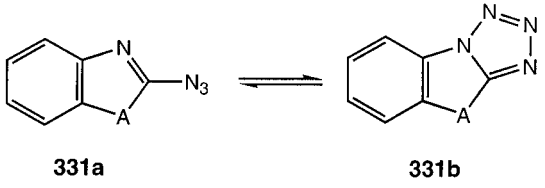


328a 328b

SCHEME 124



329 330



331a **331b**

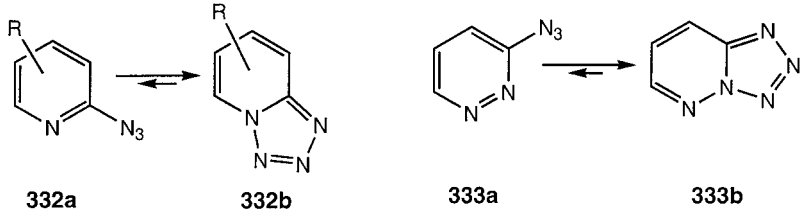
SCHEME 125

As follows from the data considered above and those collected in Table IX, the relative stability of azidoazole and tetrazoloazole tautomers may be correlated with the basicity of the nitrogen center in the azole ring, which donates its electron lone pair for the formation of a bond closing the tetrazole ring. The higher the basicity of this center the greater is the content of the tetrazole form. Thus, for benzoxazole and benzimidazole derivatives **331** with electronegative centers A = O and NH respectively, only azide forms **331a** are found in the solid state, whereas in the case of benzothiazole (A = S) and benzoselenazole (A = Se) derivatives tricyclic tetrazole tautomers **331b** are predominant (Scheme 125).

3. *Azidoazines*

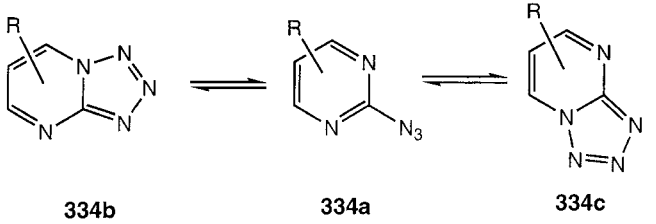
sp^2-Hybridized nitrogen centers of azines are usually more basic than those of azoles. As a consequence, azido–tetrazole tautomeric equilibria in the azidoazines are frequently shifted to cyclic tetrazole forms [73CIL371, 73S123; 75UK1028; 77AHC(21)323; 94JPR311]. Such **332b**- and **333b**-type structures are found in the solid state for tetrazolo[5,1-*a*]pyridines [77AHC(21)323] and a pyridazine analog (Scheme 126) [78AX(B)1136].

Cyclic tetrazole forms **334b** ⇌ **334c** also predominate (81–90%) in crystals of 2-azido-5-alkylpyrimidines [70T4969; 80AG(E)924; 86AG381] and in DMSO-d_6 and acetone solutions of 2-azidopyrimidine (70T4969; 88MRC42) and 2-azido-4-methylpyrimidine (Scheme 127) (90KGS1648). In $CDCl_3$, mixtures of azide and tetrazole tautomers are usually observed with the equilibrium position depending strongly on the nature of the substituent R:



332a **332b** **333a** **333b**

SCHEME 126



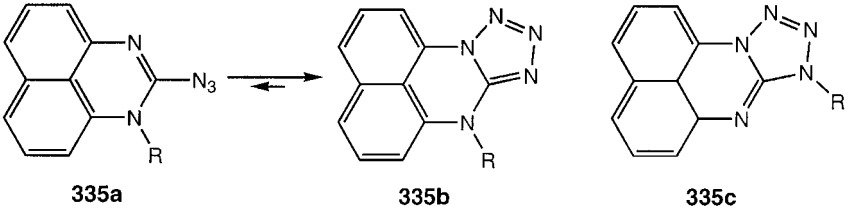
334b **334a** **334c**

SCHEME 127

the electron-withdrawing group favors the azido form **334a** (70T4969; 73S123; 88MRC42).

Cyclization of 4(6)-substituted 2-azidopyrimidines can lead to either of two cyclic tautomers **334b** and **334c.** As shown by ^{13}C-NMR (90KGS1648) and ^{15}N NMR [80AG(E)924] spectroscopy, all three tautomers coexist in solution of 2-azido-4-methylpyrimidine.

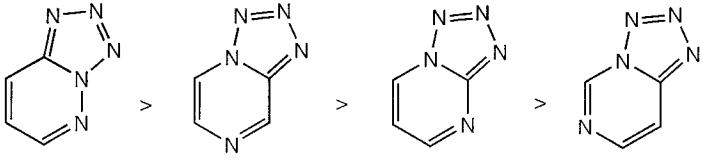
An initial conclusion that 2-azidoperimidines exist in forms of type **335a** (71KGS543) was later corrected by more detailed IR and ^{1}H NMR-spectroscopic studies (77CL1441; 81KGS1114), which established occurrence of both tautomers **335b** and **335c** (R = H) in a solution in CCl_4 (Scheme 128). Methylation of compound **335** (R = H) leads to formation of a mixture of two products: **335b** (R = Me) and **335c** (R = Me) (81KGS1114).



335a **335b** **335c**

SCHEME 128

According to (75UK1028), the relative stability of tetrazole tautomers in the isomeric tetrazoloazines increases in the sequence shown.

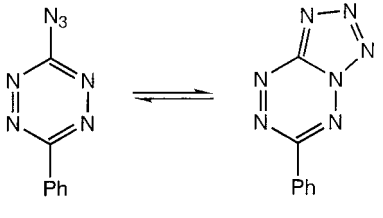


As for the azidoazoles, accumulation of electronegative nitrogen atoms in the azine ring annelated to the tetrazole fragment leads to destabilization of the tetrazole form [73CIL371, 73S123; 75UK1028; 77AHC(21)323]. Thus, 6-phenyltetrazolo[5,1-*b*]-*s*-tetrazine **336b** is a minor form in the equilibrium in *n*-hexane; however, polar solvents promote ring closure (71KGS711). Thus, the relative amount of **336b** in DMF reaches 80% (Scheme 129).

Another analogy with the behavior of the azidoazoles is the influence of substituents in various positions of the azine rings on the tautomeric equilibria. Electron-withdrawing substituents favor azidoazine and electron-releasing substituents favor tetrazoloazine forms (Table X).

This trend is well illustrated by the studies of azido–tetrazole tautomerism in the series of 2-alkyl- (70T4969) and 2-aryl-4-azidopyrimidines **337** (Scheme 130) (77IZV966; 95IZV1494). Fusion of a benzene ring to the C=C bond of the pyrimidine ring results in a strong stabilization of the tetrazole tautomer (95IZV1494). A similar trend is also observed for *s*-triazine system. Whereas 3-azido-*as*-triazines **338a** cyclize exclusively on N-2 to give the tetrazolo[1,5-*b*]-*as*-triazine **338b** (82JOC3886), 3-azidobenzo-*as*-triazines **339a** cyclize in polar solvents either on N-2 or N-4, affording an equilibrium mixture of three tautomers, with **339b′** predominating (Scheme 131). In the naphtho series of compounds, cyclization takes place on N-2 in naphtho[2,1-*e*]-*as*-triazine and naphtho[1,2-*e*]-*as*-triazine and on N-4 in naphtho[2,3-*e*]-*as*-triazine (82JOC3168; 84JOC3199). These results were well reproduced by MNDO calculations modified for the presence of vicinal sp^2 nitrogen atoms (85JOC4894).

Another interesting example of the influence of substituents on the position of azido–tetrazole tautomeric equilibria is *s*-triazolo[4,3-*c*]tetrazolo[1,5-*a*]pyrimidines **340b** (Scheme 132) (78TL1311). When the aromatic ring contains electron-withdrawing substituents (R = Cl, NO_2, CN), only the azido tautomer **340a** was found in solution of trifluoroacetic acid at room temperature. However, when the pyrimidine ring contained such substituents as CH_3 or OCH_3, the tricyclic form **340b** dominated in CF_3COOH, DMSO, and DMF solution and in the solid state.



336a **336b**

SCHEME 129

TABLE X

AZIDOAZINE–TETRAZOLOAZINE TAUTOMERISM (A–T) AS STUDIED BY NMR SPECTROSCOPY

Compounds	Method	Solvent	Temperature(°C)	K_T = [A]/[T]	References
332					
R = 5-NO_2	^{1}H NMR	$CDCl_3$	23	0.83	71T5121
		$CDCl_3$	40	1.04	71T5121
		$CDCl_3$	60	1.15	71T5121
		TFA	23	3.84	71T5121
R = 6-Cl		DMSO-d_6	25	2.51	71T5121
		DMSO-d_6	57	4.32	71T5121
		DMSO-d_6	80	6.37	71T5121
		$CDCl_3$	23	18	71T5121
		$CDCl_3$	40	Only azido form	71T5121
334					
R = H	^{15}N NMR	$CDCl_3$	30	4.83[a]	80AG(E)924
		DMSO-d_6	30	0.05	80AG(E)924
	^{1}H, ^{13}C NMR	$CDCl_3$	23–25	3.62[a]	90KGS1648
		CD_3COCD_3	23–25	0.22[b]	90KGS1648
		CD_3OD	23–25	0.33[b]	90KGS1648
		DMSO-d_6	23–25	0.05[b]	90KGS1648
		DMSO-d_6	37–38	0.07[a]	65JOC826
R = 4-Me	^{1}H, ^{13}C NMR	CCl_4	23-25	2.3[c]	90KGS1648
		$CDCl_3$	23–25	0.82[c]	90KGS1648
		CD_3COCD_3	23–25	0.09[c]	90KGS1648
		CD_3OD	23–25	0.12[c]	90KGS1648
		DMSO-d_6	23–25	0.02[c]	90KGS1648
	IR	Solid	23–25	~0.	90KGS1648

(*continues*)

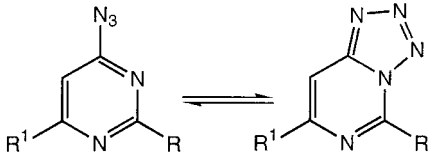
TABLE X

AZIDOAZINE–TETRAZOLOAZINE TAUTOMERISM (A–T) AS STUDIED BY NMR SPECTROSCOPY

Compounds	Method	Solvent	Temperature(°C)	K_T = [A]/[T]	References
R = 6-Me	^{15}N NMR	$CDCl_3$	30	2.63	80AG(E)924
		DMSO-d_6	30	0.06	80AG(E)924
R = 6-Et	^{15}N NMR	$CDCl_3$	30	0.59	80AG(E)924
		DMSO-d_6	30	0.06	80AG(E)924
		Solid	–	0.11	80AG(E)924
R = 6-*n*-Pr	^{15}N NMR	$CDCl_3$	30	0.57	80AG(E)924
		DMSO-d_6	30	0.07	80AG(E)924
		Solid	–	0.24	80AG(E)924
R = 6-*i*-Pr	^{15}N NMR	$CDCl_3$	30	0.25	80AG(E)924
		DMSO-d_6	30	0.05	80AG(E)924
R = 6-*n*-Bu	^{15}N NMR	$CDCl_3$	30	0.85	80AG(E)924
		DMSO-d_6	30	0.07	80AG(E)924
		Solid	–	0.19	80AG(E)924
R = 4,6-diMe	^{1}H NMR	$CDCl_3$	37–38	0.36	64JA2946, 65JOC826
	^{1}H, ^{13}C NMR	$CDCl_3$	23–25	0.22[a]	90KGS1648
		Py	37–38	0.14	64JA2946; 65JOC826
		CD_3COCD_3	37–38	0.08	64JA2946; 65JOC826
		CD_3COCD_3	23–25	0.04	90KGS1648
		CD_3OD	23–25	0.05	90KGS1648
		DMSO-d_6	23–25	~0.01	90KGS1648
337					
R = C_6H_5, R^1 = H	^{1}H NMR	$CDCl_3$	22	5.66	95IZV1494
		CD_3COCD_3	22	2.58	95IZV1494
		DMSO-d_6	22	0.66	95IZV1494

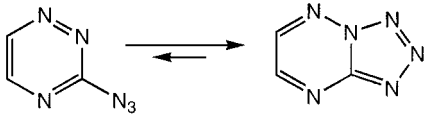
R = C_6H_4OMe-2, R^1 = H		$CDCl_3$	22	0.18	95IZV1494
		CD_3COCD_3	22	0.05	95IZV1494
		DMSO-d_6	22	0.02	95IZV1494
R = C_6H_4OH-4, R^1 = H	^{1}H NMR	$CDCl_3$	22	2.58	95IZV1494
		CD_3COCD_3	22	1.00	95IZV1494
		DMSO-d_6	22	0.28	95IZV1494
R = C_6H_4OMe-4, R^1 = H		$CDCl_3$	22	2.23	95IZV1494
		CD_3COCD_3	22	1.33	95IZV1494
		DMSO-d_6	22	0.39	95IZV1494
R = C_6H_4Br-4, R^1 = H	^{1}H NMR	$CDCl_3$	22	10.11	95IZV1494
		CD_3COCD_3	22	4.88	95IZV1494
		DMSO-d_6	22	1.27	95IZV1494
R = H, R^1 = C_6H_5		$CDCl_3$	22	1.44	95IZV1494
R = H, R^1 = C_6H_5		CD_3COCD_3	22	0.25	95IZV1494
		DMSO-d_6	22	0.03	95IZV1494
R = H, R^1 = C_6H_4OH-2		$CDCl_3$	22	Only azido form	95IZV1494
		CD_3COCD_3	22	4.00	95IZV1494
		DMSO-d_6	22	0.15	95IZV1494
		CD_3CN	22	3.35	95IZV1494
		DMF-d_7	22	0.39	95IZV1494
R = H, R^1 = C_6H_4OMe-2		$CDCl_3$	22	0.82	95IZV1494
R = H, R^1 = C_6H_4OMe-4		$CDCl_3$	22	1.33	95IZV1494
		CD_3COCD_3	22	0.27	95IZV1494

[a] K_T = [**334a**]/[**334b**].
[b] K_T = [**334a**]/[**334c**].
[c] K_T = [**334a**]/[**334b**] + [**334c**].

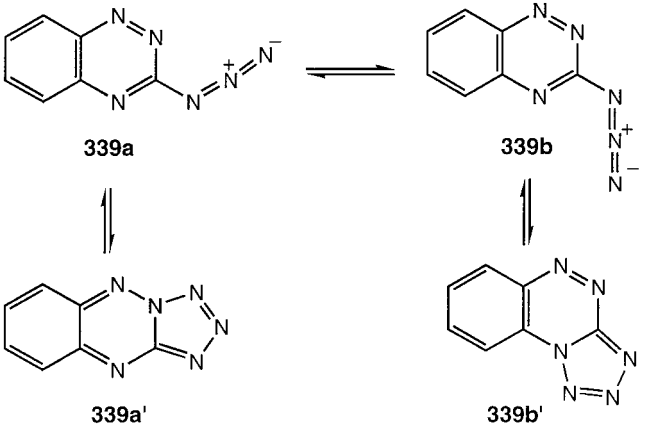


337a **337b**

SCHEME 130



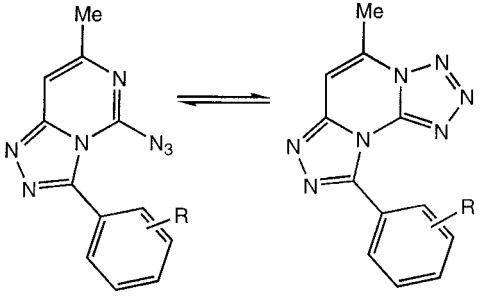
338a **338b**



339a **339b**

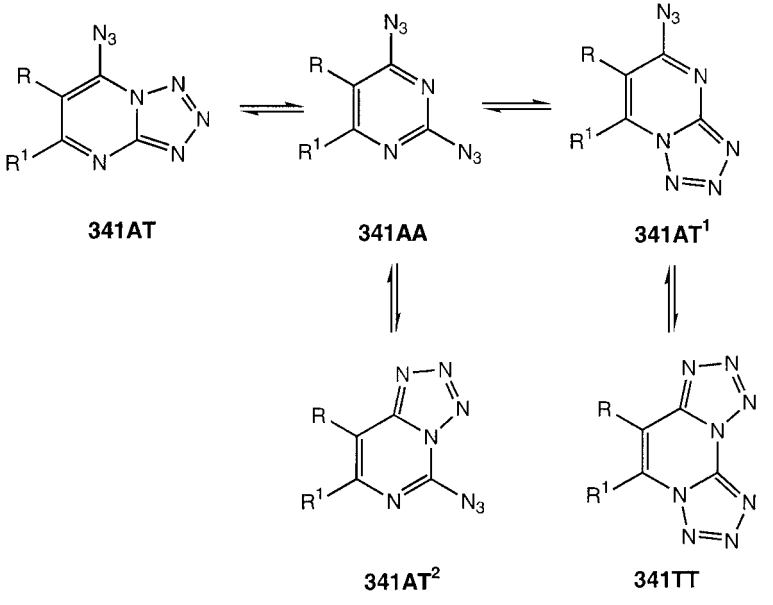
339a' **339b'**

SCHEME 131



340a **340b**

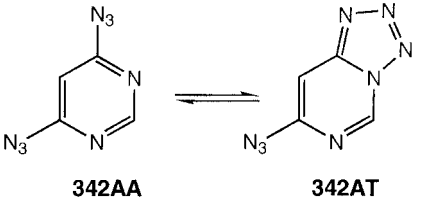
SCHEME 132



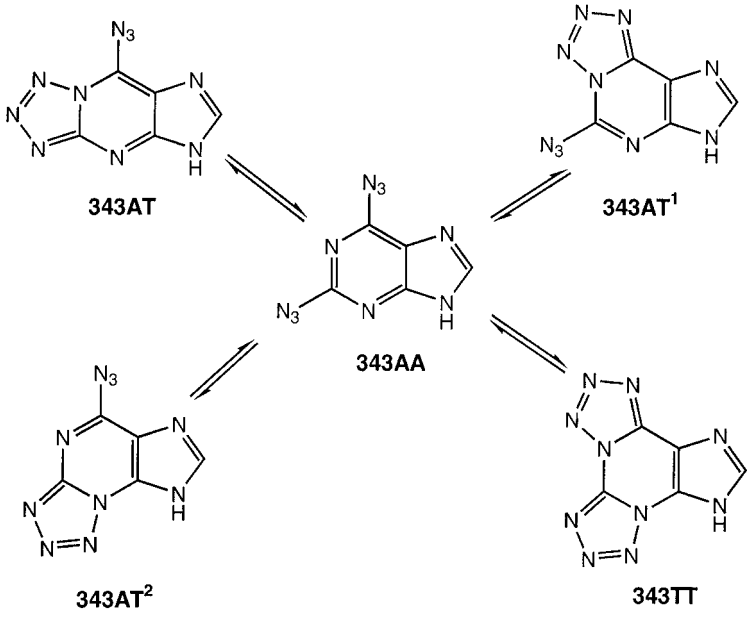
SCHEME 133

The case of azido–tetrazole tautomerism of azines containing two and three azido groups in the ring is of special interest. For 2,4-diazidopyrimidine, five isomers can potentially participate in the tautomeric equilibrium (86IZV1916; 88DOK115). Three of them, **341AA, 341AT** and **341TT** (R = R^1 = H), were found to coexist in a ratio depending on the nature of solvent and temperature in solutions of acetone-d_6, DMF-d_7, and DMSO-d_6 (Scheme 133). In $CDCl_3$ solution, two tautomers **341AA** and **341AT** were observed in the ratio of 88 : 12. In the solid, the compound exists as a sole **341AT** tautomer as was proven by an X-ray crystallographic study (88DOK115).

In contrast to the 2,4-diazidopyrimidines, only one azido group is involved in ring-chain transformations of 4,6-diazidopyrimidine **342** (Scheme 134) (88DOK115). The content of the tetrazole tautomer **342AT** increases



SCHEME 134



SCHEME 135

with increase in polarity of the solvent: 3% in $CDCl_3$, 26% in acetone-d_6, and 73% in DMSO-d_6.

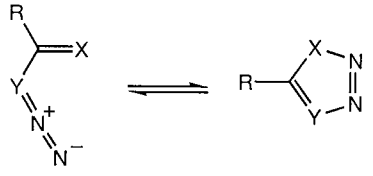
Five possible isomers may coexist in the tautomeric equilibrium involving 2,6-diazidopurine **343** (Scheme 135). It was concluded (75UK1028) that diazide **343AA** is the sole form in the solid state and in solutions in acetic and trifluoroacetic acids. In DMSO solution, two additional tautomers, **343AT** and **343AT[1],** were also observed.

No tetrazolo species were found in solutions of 2,4,6-triazido-*s*-triazine and 2,4,6-triazidopyrimidine (79UKZ975).

4. *Azido*-v-*Triazole and Diazido–Azole Isomerizations*

The azidoazomethine–tetrazole tautomerism **344a** ⇌ **344b** considered in the previous sections is the most important member of a family of valence isomerizations of the general type **344** where Y and X groups may be met in various combinations (Scheme 136).

Ring closure of vinyl azides **344a** (X = CHR^1, Y = N) to 4*H*-v-triazoles **344b** (X = CHR^1, Y = N) is a step in the thermolysis of vinyl azides leading to azirines. According to *ab initio* RHF/4-31G calculations (78JA3668) the energy gap between the more stable parent 4*H*-1,2,3-triazole **344b** (X = CH_2, Y = N) and vinyl azide **344a** (X = CH_2, Y = N) is as large as 45.2 kJ



344a **344b**

X = CHR^1, NR^1, O, S

Y = N, CR^2

SCHEME 136

mol^{-1} and the energy barrier to the **344a** ⇌ **344b** isomerization is 172.4 kJ mol^{-1}. These values are out of the normal limit of the energy scale of tautomeric processes. Other known azido-*v*-triazole valence isomerizations also do not involve equilibria of the isomers **344a** and **344b** and thus should not be classified as the tautomeric processes [74JOC1778; 76AHC(S1), p. 498].

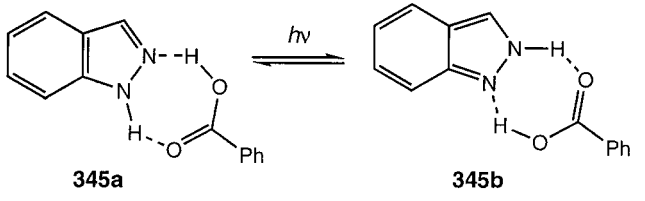
This conclusion is valid also for the isomerizations involving cyclization of diazides **344a** (R = N_3, Y = CH) [74JOC1778; 76AHC(S1), p. 498]. Thermodynamic and kinetic parameters of type **344a** ⇌ **344b** interconversion are modified by the substituents R and R^1, which means that under certain conditions the isomerization may be considered as tautomerization.

V. Tautomeric Transformations in the Electronic Excited States

Acidities and relative stabilities of tautomers can be radically changed on electronic excitation resulting in significant shifts in the tautomeric equilibrium between ground and excited states. Lifetimes of molecules in their electronic excited states are short: 10^{-3} to 10 s for triplet and 10^{-7} to 10^{-10} s for singlet states (69MI1). Therefore, specific methods must be employed for the detection and observation of individual tautomers in the electronic excited states. These primarily include high-resolution and time-resolved emission and transient absorption spectroscopy and electronic paramagnetic resonance.

A. Annular Tautomerism

An example of a shift in the annular tautomeric equilibrium occurring through electronic excitation is represented by the case of the lowest triplet



345a **345b**

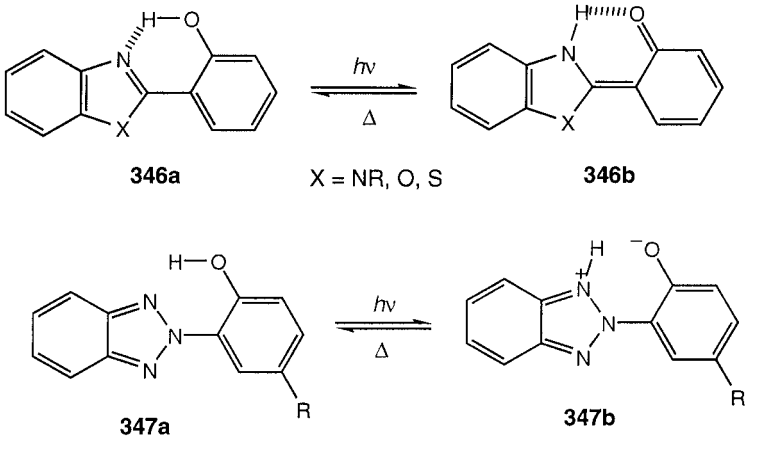
SCHEME 137

state of indazole. In a benzoic acid host, the phosphorescence spectrum of indazole consists of bands belonging to both 1*H* and 2*H* tautomeric forms whose different decomposition pathways and magnetic properties were determined by the EPR and ODMR experiments (Scheme 137) (83JA6790). It was assumed that a tautomeric rearrangement of the 1*H* tautomer to the 2*H* form, which does not exist in the ground state, occurs in the excited state as a double proton switching along the hydrogen bonds in the indazole–benzoic acid H-complexes. The orientations of the two tautomers in benzoic acid were determined from the angular dependence of the EPR signals. Similar double-proton transfers in excited cyclic dimers of azaindoles is a thoroughly studied phenomenon (87JA1346; 95NAT260).

B. PHOTOTAUTOMERIZATION OF *o*-HYDROXYPHENYLAZOLES

o-Hydroxyphenylazoles represent an important group of photostabilizer additives for polymeric materials and laser dyes. These properties are caused by the ability of the compounds to undergo the tautomeric transformation through a facile intramolecular proton transfer which occurs in the first electronic excited state.

The tautomers **346b** and **347b** formed possess very short lifetimes and were initially identified by their fluorescences which display a large Stokes shift relative to the absorption of the stable enol tautomers **346a** and **347a** (Scheme 138) (67ZPK641; 70JPC4473; 76DOK126; 98UK140). Thus, the compounds **346** and **347** should be assigned to the so-called ESIPT (excited state intramolecular proton transfer) systems first described by Weller (56ZE1144) on the example of methyl salicylate. Recent reviews (89JPC29; 90MI1; 91JPC10215) of the heteroaromatic molecules exhibiting ESIPT include 5-aryl-2-(2′-hydroxyphenyl)oxazole (97MI388), 2-(2′-hydroyphenyl) benzoxazole **346** (X = O) (see also 92CP43; 95JPC12456), the corresponding benzothiazole **346** (X = S) and benzimidazole **346** (X = NH) [see also 99JPC(A)4525], 2-(3′-hydroxy-2′-pyridyl)benzimidazole (see also 94JPC8666), and 2,5-bis(benzazol-2′-yl)hydroquinones [92JCP3914; 97JCS(P2)1861; 98UK140].



SCHEME 138

Rapid nonradiative (K^{b}_{nr}) degradation supplements the radiative (K^{b}_{r}) $S_1 - S_0$ conversion of the tautomers **346b** and **347b** and back-transfer of the proton recovers the original S_0–enol structures **346a** and **347a.** Figure 1 portrays a general four-level diagram that depicts the phototautomerism of *o*-hydroxyphenylazoles. For the sake of simplicity, the scheme does not portray the frequent involvement in the photophysical cycle of the lowest triplet levels of the interconverting tautomers [88CPL112; 92JCS(CC)641; 93JPC306].

The closed cycle of interconversions occurs on an ultrafast time scale. Femtosecond studies (95CPL35) of the ESIPT rearrangement of **347** (R = Me) (commercial name Tinuvin-P) carried out over a wide spectral range

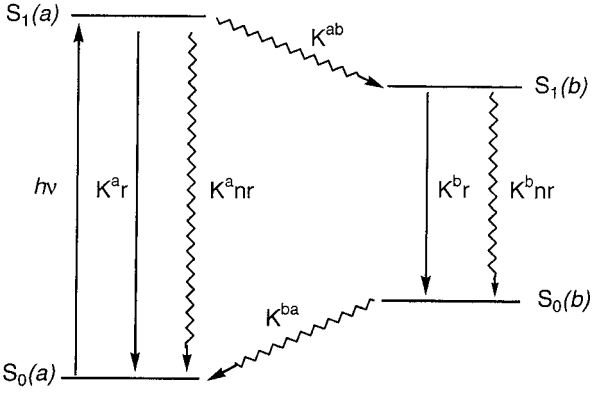
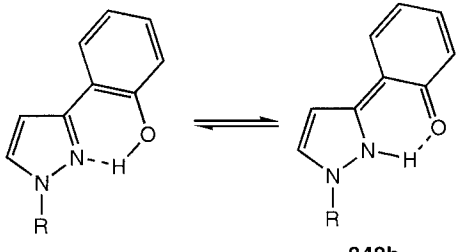


FIG. 1. Four-level diagram for the phototautomerism of *o*-hydroxyphenylazoles.

showed that the isomer **347b** was produced on a 100-fs time scale upon excitation of **347a.** It degrades with a time constant of 150 fs due to the internal conversion (K_r^b) to the ground state and approximately 600 fs for the proton back-transfer to the enol ground state. These findings point to a negligible barrier along the reaction pathway in the excited state, which is in accord with experiments on the phototautomeric fluorescence study of the proton-transfer rate showing rate constants of the order 10^{10} s^{-1} in 2,5-bis(benzoxazolyl)hydroquinone (91CPL17) and the observed absence of fluorescence from the tautomer **347a** in solid argon matrices at 15 K (87BBPC1205). A sharp reduction in the barrier to proton transfer in the singlet excited state was explained by the results of *ab initio* CIS/3-21G* calculations of the ESIPT in **346** (X = O) that revealed significant shortening of the O···N distance in the singlet excited state of **346a** as compared to that in the ground state (95JPC12456). Calculations (97JA5445) performed at the same level of approximation for 2-(2′-hydroxyphenyl)benzotriazole **347** (R = H) afforded, in addition to the planar tautomer **347b,** another folded structure of the singlet excited state which is only 1.5 kJ mol^{-1} higher in energy. The S_0–S_1 energy gap in this structure is significantly narrower than that at the planar geometry, which provides for intersection of the two surfaces and facilitates internal conversion by nonradiative mechanism. The occurrence of two types of phototautomers ascribed to planar and twisted conformers was also suggested for **346** (X = S) (85JA1561). The extreme sensitivity of the rates of dissipation of the energy of the exciting photon in the ESIPT systems to temperature, viscosity, and other environmental effects has been emphasized (90MI1; 94JPC8666; 95JPC17711).

The ESIPT mechanism of phototautomerization allows the employment of types **346** and **347** compounds and their analogs as UV stabilizers useful for synthetic polymers. Such a stabilizer rapidly converts the energy ab-



348a **348b**

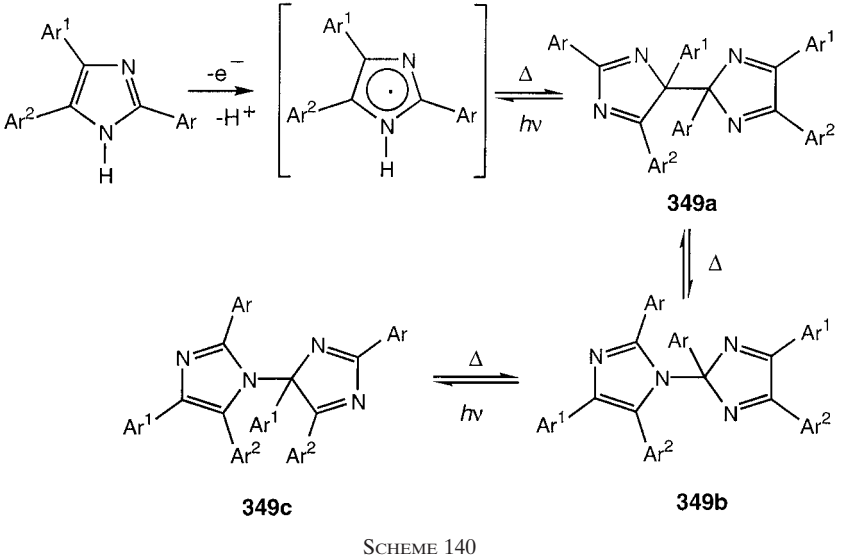
SCHEME 139

sorbed from sunlight into thermal vibrational energy of the ground-state tautomer, thus preventing photodegradation (90MI1). A new class of UV stabilizers, the *C*-(2′-hydroxyphenyl)pyrazoles **348** has been recently described (Scheme 139) (92JA5039). The compounds are susceptible to proton transfer in the first excited singlet states of the enol tautomers. The photostability of some of them exceeds that of Tinuvin-P.

C. Tautomerism and Photochromism by Homolytic Cleavage in Triarylimidazole Dimers

A peculiar case of fast and reversible (i.e., tautomeric) isomerizations initiated thermally or photochemically is represented by triarylimidazole dimers **349a** formed by oxidation of triarylimidazoles (66JA3825; 90MI2) and diarylhetarylimidazoles (Ar = Het) (Scheme 140) [97MI553].

Initially formed dimers **349a** rearrange to **349b** during crystallization from benzene or cyclohexane. Heating **349b** results in an equilibrium mixture of three isomers, and **349b** and **349c** are also interconvertible by UV irradiation. Three other dimeric structures are also possible, but were not unambiguously identified.

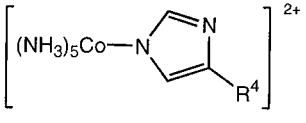


Scheme 140

VI. Stabilization of Unusual Tautomeric Forms of Azoles and Their Derivatives in Metal Coordination Compounds

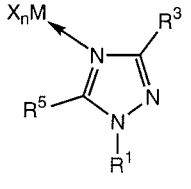
A. Annular Tautomers

On complexation with metal ions, donation of an electron pair of a pyridinelike nitrogen to the metal center leads to fixation of the fluctuating proton at a certain position of the azole ring. Substitution of this proton by a metal centered ion may also result in a metal coordination compound which is not necessarily the derivative of the predominant prototropic tautomer. Such a stabilization of a particular tautomeric form or its derivative has been widely studied for pyrazoles (Chapter 1, Section XI); imidazoles **350** [83IC2693; 91JCS(D)3031]; 1,2,4-triazoles **351** (84IC1404; 91IC4038); benzo-1,2,3-triazole **352** [81ACS(A)733; 94POL1593]; and tetrazoles **353** (94POL2929) and **354** [82IC834; 83AX(C)567, 83IC1205; 90IC3806; 91IC3707; 93IC2394; 94IC1921].



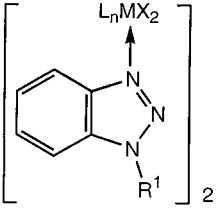
350

R^4 = Me, Br



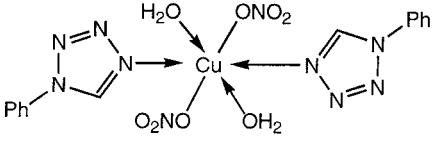
351

R^1 = H, R^3 = H, α-Py, alkyl
R^5 = H, Ph, alkyl

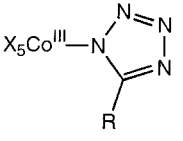


352

R^1 = H, Me;
L = H_2O, MeOH, MeCOMe;
n = 0 - 2
M = Cu, Ni

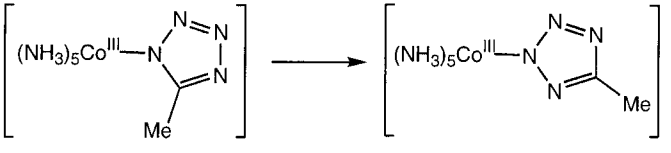


353



354: X = CN, NH_3

In some cases, e.g., **355** → **356,** formation of the stable form is preceded by a rearrangement of the initially formed metal complex (91IC3707; 94IC1921) (Scheme 141).



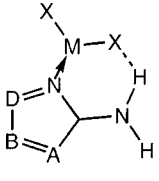
355 356

SCHEME 141

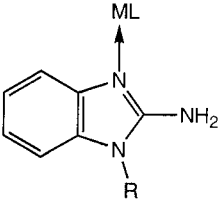
B. AZOLES WITH POTENTIALLY TAUTOMERIC SUBSTITUENTS

1. *Aminoazoles*

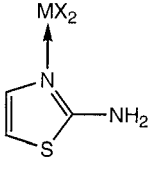
Aminoazole ligands in their metal complexes usually retain their amino structure, metal atoms being coordinated at the endocyclic nitrogen centers [73UK177; 87DOK1119; 93KK566; 94RJCC77, 94KK83; 97UK434; 98AHC (72)1, 98KK215]. However, the mode of binding depends strongly on the nature of the metal atom. For example, N_{ring} binding predominates among 3-amino-5-methylisoxazole complexes with the most metals; however, Pd, Pt, Cd, and Zn are complexed with the ring oxygen, while Ni favors N_{amino} complexation [91CCR251].



357: A = NR, O, S
B, D = CR, N
R = H, alkyl, aryl



358



359

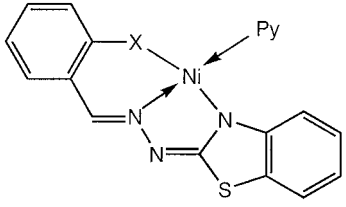
Structures **357** have been proven for the aminoazole complexes by their IR (94RJCC77, 94KK83) and NMR (86KK1244) spectra and quantum mechanical calculations (95IZV2378, 95RJCC654; 96KK510).

X-Ray structural determinations were performed for metal complexes of derivatives of 2-aminobenzimidazole **358** (R = C_7H_{15}, M = Cu, L = $(AcO)_2$ (89ICA177); R = Me, M = Cu, L = tosylaminosalicylideneaniline (96IZV2093)) and 2-aminothiazole **359** (M = Cu, X = AcO [89ZSK(6)155]; M = Zn, X = Cl [93AX(C)592]).

The main factors providing for the amino structure of the complexes **357–359** are relatively low acidity of the amino groups in aminoazoles and

the higher ability of the endocyclic nitrogens to localize the coordination bond [94KK83, 94RJCC77; 97UK434; 98AHC(72)1].

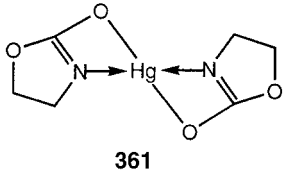
In contrast with aminoazole ligands, hydrazones of azoles adopt the imino form in their metal complexes **360** [X = O (93ZNK863), X = S (91MC110)].



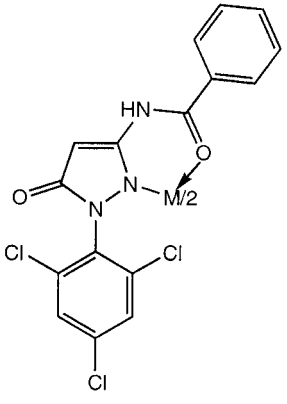
360: X = O, S

2. *Hydroxyazoles*

Due to the relatively high acidities of their hydroxy groups, hydroxyazoles readily exchange their protons with metal ions, which leads to stabilization of metal derivatives of the hydroxy tautomeric forms in metal coordination compounds of 2(5)-oxoazoles [97UK434; 98AHC(72)1]. A typical example is the mercury complex **361** [93JCS(D)1003].



361

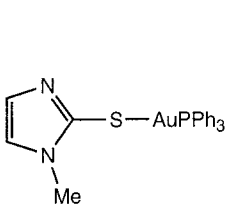


362

Another type of tautomerization was observed in the complexation reaction of 5-oxo tautomers of pyrazolone with metal chlorides **362** (89ZNK 2966).

3. *Mercaptoazoles*

The thiol form, uncharacteristic for free mercaptoazoles, was found to be realized in their metal complexes [85CCR115; 96MI19; 97UK434; 98AHC (72)1, 98CCR31]. X-Ray structural evidences of the thiol form of ligands have been presented for the complexes **363** [88JOM(344)119] and the copper cluster $\{Cu^{I}_{10}Cu^{II}_{2}(C_4H_5N_2S)_{12}(MeCN)_4\}$ [80JCS(CC)867] containing the 2-mercaptoimidazole fragment **364.**



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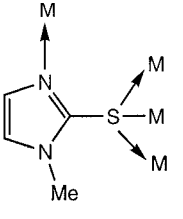
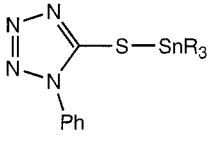
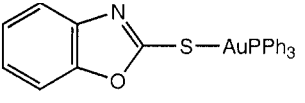


364

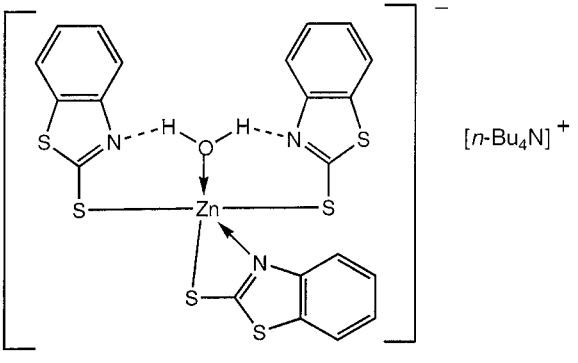
Similar coordination sites are found also in several other metal complexes with *N*-phenyltetrazole **365** [94JOM(482)147, 94JOM(484)33, 94POL2809; 96JOM(513)63]; benzoxazole **366** [89AX(C)1420]; and benzothiazole **367** [85CCR115; 96CCR199; 98AHC(72)1, 98CCR31], **368** (93POL2241), and **369** (96POL2127) ligands.



365



366



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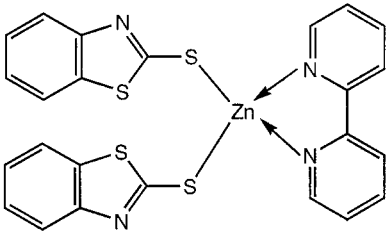
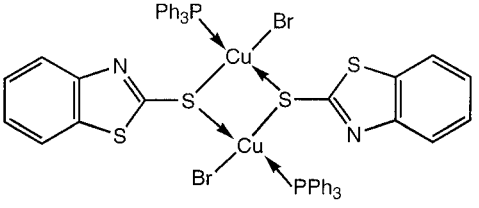
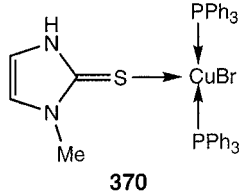


368



369

However, the thione form of mercaptoazole ligands is retained in the metal complexes of 1-methyl-1,3-imidazolin-2-thione **370** (90POL981) and **371** [92ICA75; 93JOM(453)47], 1-phenyltetrazol-5-thione **372** [96JOM (513)63]; and 1,3-thiazolidin-2-thione **373** (89ICA265).



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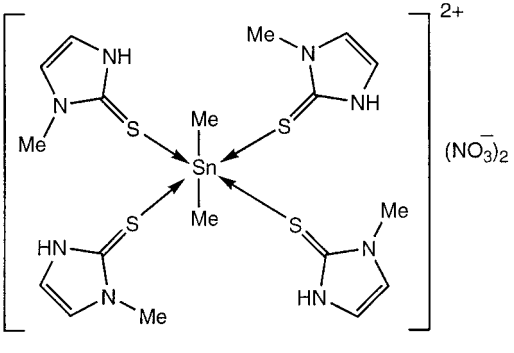

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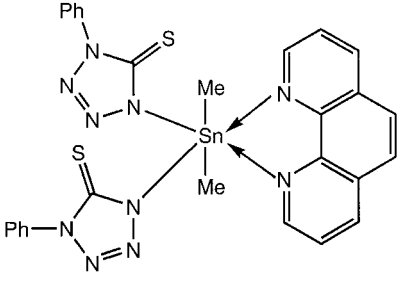
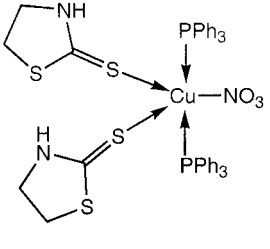
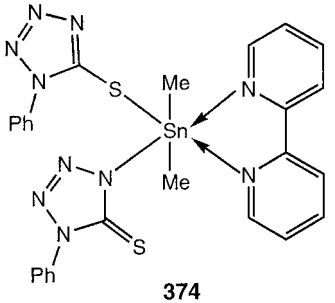


372



373

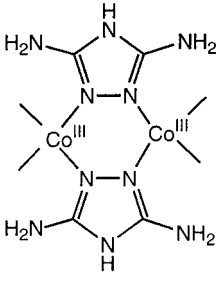
In the complex **374,** formed by 1-phenyltetrazol-5-thione with dimethyltin, both thiol and thione types of coordination bonds were found using X-rays [96JOM(513)63].



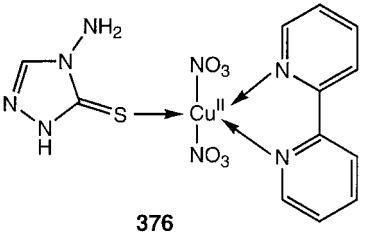
374

4. *Azoles with Two Potentially Tautomeric Exocyclic Groups*

According to X-ray data, 2,5-diamino-1,3,4-triazole retains its diamino form in the heterovalent cobalt complex **375** (91IC4858) and in the polymeric complex with manganese thiocyanate (93ICA53).

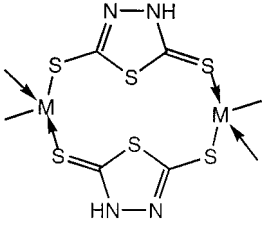


375



376

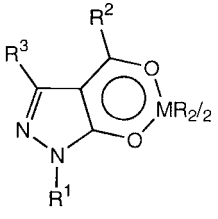
The 4-amino-3-methyl-1,2,4-Ä^2-triazoline-5-thiol ligand, which exists in its thione form in the crystal [90JCR(S)214], was found to preserve the same form in the complexes **376** (96ACSA596). The mixed thione–thiol form of 2,5-dimercapto-1,3,4-thiadiazole has been attributed to this ligand in its complexes **377** (75JINC1804; 77JINC581) on the basis of the IR-spectroscopic studies. Such an assignment should not be considered definitive (96UK326).



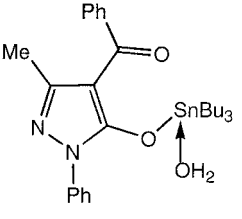
377

5. *Azoles with Potentially Tautomeric Chelated Substituents*

For most metal complexes of vicinal hydroxyacylpyrazoles **248** (A = NR^1, X = O) the molecular structure is similar to that in the free ligands and 1,3-diketones (78MI1; 97UK434) with significantly delocalized bonds within the chelate ring. Organotin [91JOM(405)75; 93JOM(458)39; 94JOM (483)123, 94POL939; 96JOM(519)29; 98MI236] and organocopper (89IC3014) chelates **378** are well-studied examples.



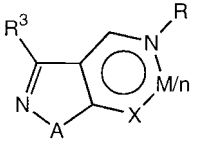
378: R = Me, Bu
R^1, R^2 = Me, Ar
R^3 = Me, Ph
M = Cu, Sn



379

The nonchelated structure that conforms to the hydroxy tautomeric form of the ligand **248a** has been found in the hydrate **379** [96JOM(511)227].

Whereas vicinal hydroxy, mercapto, and hydroselenoaldimines of azoles strongly prefer the aminomethylene tautomeric form (Section II,E,2), their metal chelates **380** are characterized by pronounced equalization of bond lengths within the chelate ring, which makes their structures similar to those expected for the aldimine tautomeric type.

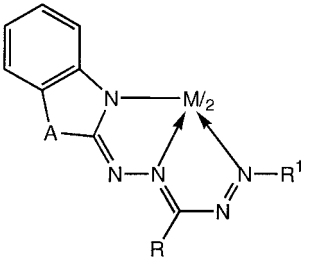


380: X = O, S, Se
A = NR^1, O

X-Ray structural determinations were carried out for an array of pyrazole complexes **380** (A = NR^1; R = Alk, Ar, Het; R^3 = Alk, Ar; X = S, Se; M = Ni, Pd, Cu, Zn, Cd, Hg [93CCR1; 97CCR191]). Special attention has been given to iron [96MI255; 97DOK212, 97JCS(CC)1711] and copper (92MC30; 97CCR191; 99DOK67) complexes, the structures of which model

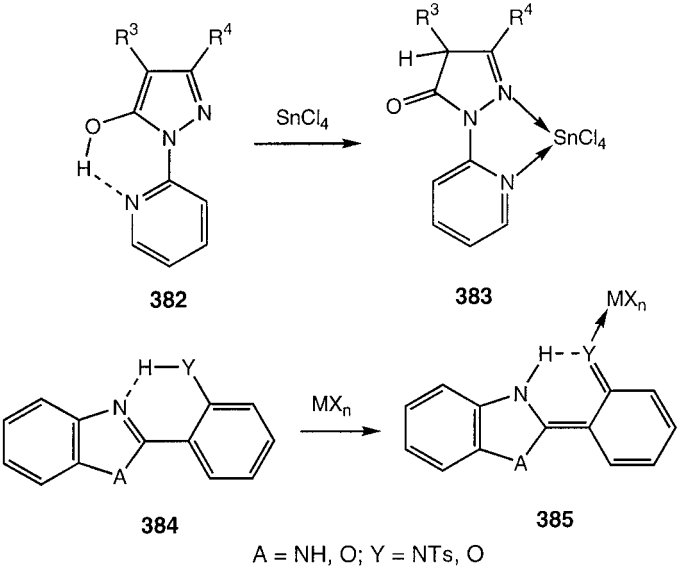
the active centers of nonporphyrin metal proteins (96MI255; 97CCR191) and also stereochemically nonrigid tetrahedral complexes of nontransition metals (94UK303; 96MI8, 96MI12).

As proven by ^{13}C NMR spectroscopy (92KK312; 93KK215; 95KGS1269; 96MI230) and X-ray crystallography (93KK215, 93KK904), the ligands in complexes of benzothiazolyl formazanes **381** (A = S) adopt nontypical imino tautomeric forms (96MI230).



381

Examples of the fixation of very minor prototropic tautomeric forms on complexation are known in the series of complexes of 1-(2′-pyridyl)-5-hydroxypyrazoles **383** [76AHC(S1), p. 333; 70ZOB1114] and 2-[2′-hydroxy (*N*-tosylaminophenyl)]benzazoles **385** (Scheme 142) (98ZOB496).



382 **383**

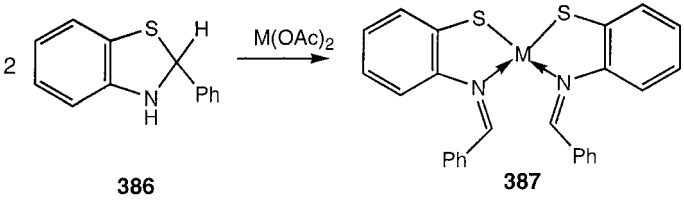
384 **385**

A = NH, O; Y = NTs, O

SCHEME 142

C. Ligands Susceptible to Ring-Chain and Azide–Tetrazole Tautomerism

Interaction with metal ions facilitates ring-opening reactions and provides for fixation of ligands in the complexes thus formed in structures characteristic of minor ring-opened forms. Thus, benzothiazolines **386** [87RRC151; 90T6545; 93CCR1; 96AHC(66)1, 96CHEC-II(3)373; 97BCJ1599] on reaction with metal acetates afford the complexes **387** [M = Ni (75IZV2130, 92CL893, 97BCJ1599), Pd (92CL297)], with structures proven by X-ray crystallography (Scheme 143).

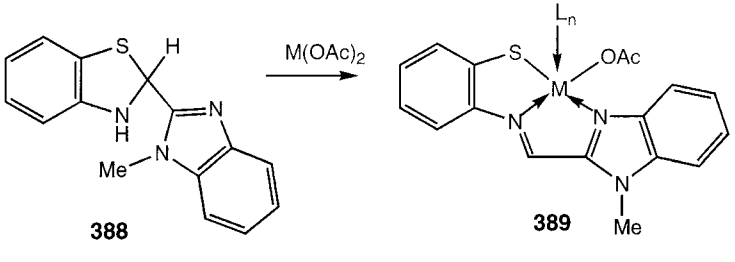


386 **387**

Scheme 143

Stabilization of a metal-substituted derivative of a minor tautomeric form of the ligand was reported for the complexes of mixed benzothiazoline–benzimidazole (**388** → **389**) (71ZOB1370; 98POL381) and benzothiazoline–pyridine ligands (**390** → **391/392**) (Scheme 144) (77JA7704).

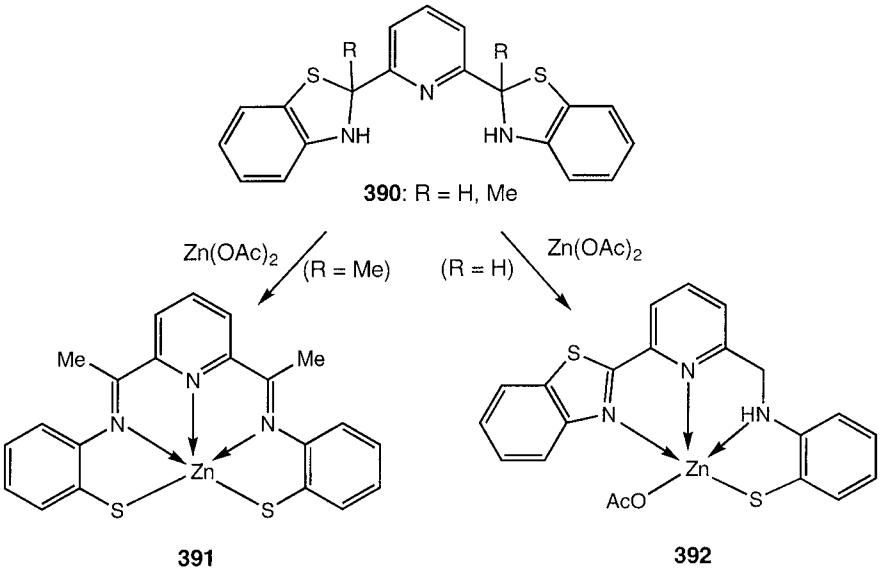
Another transformation of this type is a conversion of the ring-closed form **393** to the derivative of aroylhydrazone of acetylacetone **394** (Scheme 145) (81KK1165; 92KK1184).



388 **389**

M = Co, Ni, Pd, Zn, Cd; L = H_2O, MeOH; n = 0 - 2

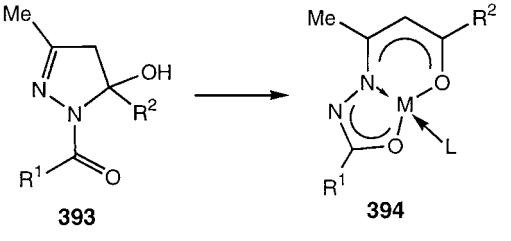
Scheme 144



SCHEME 144 *Continued*

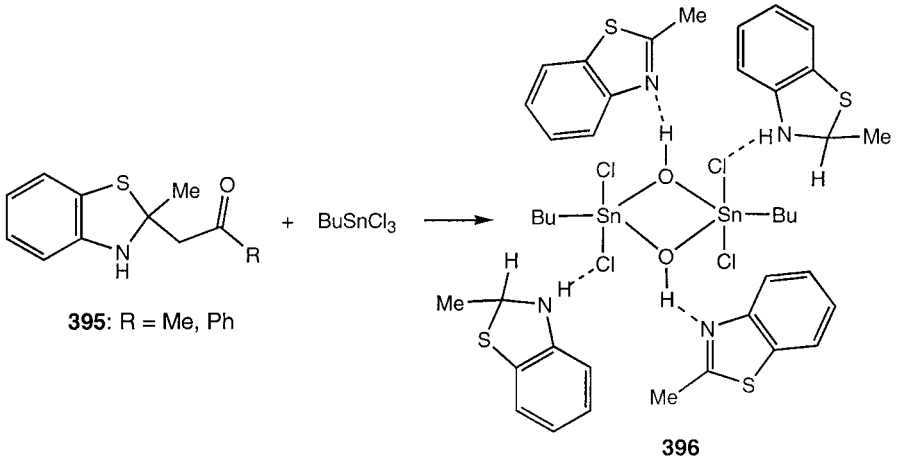
Ring-opening is not a mandatory direction of the complexation reaction. Thus, the ring-closed form of the benzothiazoline **395** ligand was found to be preserved in its complex **396** with $BuSnCl_3$, whose structure was determined with X-rays (Scheme 146) [93JOM(454)67].

Benzo-1,3-thiazole-2-azide reacts with metal salts to give a mixture of complexes of both possible tautomeric forms **397** and **398** (Scheme 147) (75UKZ1238). However, this conclusion was made only on analysis of the IR spectra of the reaction products and should not be considered final.

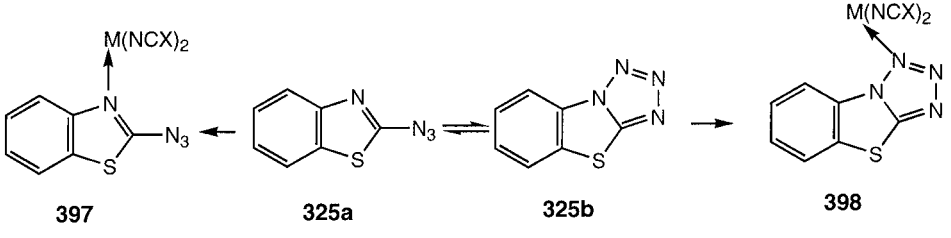


M = Cu, Zn, Ni; L = NH_3, PPh_3
R^1 = aryl; R^2 = CH_3, CF_3

SCHEME 145



SCHEME 146



SCHEME 147

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