1
Tautomerism: A Historical Perspective

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When I started my PhD Thesis, some 60 years ago, I was involved with pyrazoles tautomerism (annular of pyrazoles and indazoles and functional of pyrazolinones, then called *pyrazolones*). The knowledge about tautomerism was empirical, qualitative, and unsystematic. Owing to the efforts of Alan Roy Katritzky and those of my thesis supervisor, Robert Jacquier, the situation improved considerably resulting in the publication in 1976 of the book "The Tautomerism of Heterocycles" [1].[1)]

One can say that, in 1976, there was good understanding of the thermodynamic aspects of the tautomerism of heteroaromatic compounds as well as that of compounds like β-diketones and related structures. Besides, thanks to the works of Hammett, Taft, Exner, and many others, the influence of substituents and solvents on the equilibrium constants can be quantified through extrathermodynamic relationships.

We are now in the process of changing the paradigm and moving to a complete picture of the kinetic and thermodynamic aspects of tautomerism in the three phases, gas, solution, solid, and including ground and excited states. This is due to the increasing power of physicochemical methods as well as to the enormous success of theoretical chemistry. It is not finished yet and many inputs and many years of research will be necessary to declare that the task is completed. The subject has been reviewed in 2000 [2] and in 2014 [3] and the present book, to be published in 2016 [4], will further actualize it. An interesting effort is being made for building-up tools for the automatic generation of all tautomeric forms of a given organic compound, for instance, Ambit-Tautomer [5].

To display a panorama of tautomerism today, a practical approach is to divide the knowledge into three sections: high, medium, and low. This warrants a separation of the thermodynamic aspects from the kinetic aspects, since often the first are well known but not so much the latter.

Unless stated differently, this introduction will deal with **prototropic** tautomerism, which is by far the most common. It corresponds to the proton

1) According to Google Scholar (December 2014) this book has been cited 811 times.

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transfer between two atoms that can occur directly if the geometry allows it or occurs with the assistance of another molecule or molecules, especially, solvent ones. The first process is easily approached theoretically but the second one needs the study of supramolecular complexes that are simplified models of the reality.

1.1 Thermodynamic Aspects

1.1.1 What Is Well Known

1) ***Gas phase*:**
For many years microwave (MW) spectroscopy has been providing invaluable information about the structure of tautomers in the gas phase. However, more recently, MW spectroscopists have been able to identify several tautomers simultaneously: four tautomers of guanine [6]; two tautomers of 2-hydroxypyridine/2-pyridone microsolvated with one and two water molecules [7]; two tautomers, 1*H* and 3*H*, of 4-vinylimidazole [8]; and all five tautomers of cytosine [9]. These data are very useful for theoretical chemists, but reciprocally it should be remembered that MW spectroscopists use high-level theoretical calculations to assign their structures. A cautionary note should be added here about the problem of theoretically calculated entropic contributions and the use of the harmonic approximation [10].
Well-known aspects are the relationships between tautomerism and aromaticity due to the work of some pre-eminent authors: Katritzky *et al.* [11], Schleyer *et al.* [12], and Krygowski *et al.* [13]. Another well-understood issue is the influence of intramolecular hydrogen-bonds (IMHBs) on tautomerism [14, 15].
2) ***Solution*:**
This is the best known of all sections of this perspective [1–4]. With regard to differences in energy between tautomers, two extreme situations occur. If the difference is large, then the structure of the most abundant tautomer is easily established as it is the same in all phases although the determination of the amounts of the less stable tautomers is difficult. On the other hand, when the tautomers are present in comparable amounts, the problem is more interesting but the proportions are highly dependent on the state.
Nuclear magnetic resonance (NMR) continues to be the method of choice to study tautomerism in solution with low temperature studies becoming more common due to the use of dipolar aprotic solvents of low melting point, such as DMF-d_7 [16] and HMPA-d_{18} [17]. The main limitation of the use of NMR is due to it being a "slow method" that often needs the use of model compounds, whereas, UV-Vis spectroscopy is very fast and tautomers are seen

as individual species. Moreover, the number of solvents that can be used is almost unlimited and the range of concentrations very large (from 10^{-6} to 10^{-2} M) [18].

Since it is frequently ignored, the Gustafsson paradox should be remembered here: tautomers that act simultaneously as HB donors and acceptors have the protonated and deprotonated species in common, and thus, the less stable one shows the larger basicity and acidity simultaneously [1, 19, 20].

3) ***Solid state*:**
The number of structures of tautomers determined by X-ray crystallography (and some by neutron diffraction) is considerable [21]. An aspect of tautomerism, usually but not always studied by crystallography (silver complex of chloroquine [22]), is the effect of the coordination with metals on tautomerism. Many examples have been reported, such as: (i) 2-(1*H*-pyrazol-5-yl)phenol to 2-(1*H*-pyrazol-3-yl)phenol by coordination to a ruthenium complex [23]; (ii) 1*H*- to 2*H*-indazole when forming an osmium(IV) complex [24]; (iii) the four silver complexes of N^6-methoxyadenine imino tautomer [25]; and (iv) the pyridone to hydroxypyridine threefold-symmetric ligand tautomerization induced by CuCl [26].

1.1.2 What Needs to Be Completed

1) ***Gas phase*:**
This aspect is conveniently covered at least for the ground states.

2) ***Solution*:**
If the effect of IMHBs on tautomerism is well understood, it can be seen that this is not the case for intermolecular hydrogen bonds that occur in solution with solvents that are either hydrogen bond acceptors (HBAs), hydrogen bond donors (HBDs), or both (like water). This is partly related to the large number of possible complexes when one includes two or more solvent molecules.

An important effort is being presently done to study, both experimentally and theoretically, the excited states of compounds that exist in several tautomeric forms; for instance, the singlet and triplet excited-state dynamics of the keto and enol tautomers of **cytosine** [27], the ultrafast excited-state decay of **allopurinol** keto-N9H tautomer from gas phase to aqueous solution [28], the reduced aromaticity in **lysine-tryptophan** dipeptide (lys-trp) cations, and the fact that the high pH tautomer correlates with lower quantum yield and shorter lifetimes [29]. The structure of the compounds appear in bold to call the attention to their biological and pharmaceutical nature.

If one judges from the large number of recent papers dealing with the phenomenon of Excited State Intramolecular Proton Transfer (ESIPT) it can be stated that this topic needs further studies. The proton transfer could result in a tautomerization, for instance, in 2-pyridyl pyrazoles [30, 31].

3) ***Solid state*:**
Most authors consider tautomerism to be a minor phenomenon that can be included in polymorphism [32, 33]. This is not our opinion and we prefer to use desmotropy instead of tautomeric polymorphism [34–36]. Tautomers can also be present in co-crystals [37].
The development of periodic calculations Gauge Including Projector Augmented Waves (GIPAW) [38], Quantum Espresso [39]) both for crystallography and for solid state NMR Magic Angle Spinning (MAS) and Cross Polarization MAS (CPMAS) offers experimentalists with possibilities that are still not routinely used.

1.1.3
What Is Ill Known

1) ***Gas phase*:**
A great effort is needed to apply the knowledge obtained on the effect of HBs on tautomerism for other noncovalent interactions: chalcogen bonds [40]; halogen bonds [41, 42]; N–H· · ·π interactions [43], among others.
2) ***Solution*:**
The relationship between tautomerism and biological activity is very important, although still unclear, because no serious experimental studies have been carried out. The problem can be modeled by a host–guest situation (Figure 1.1), considering that molecular recognition forces will discriminate between tautomers.
The difficulty resides in the fact that if one modifies the guest (ligand) it is possible that not only K_1 but also the host–guest (receptor, R) affinity will be modified, depending on the nature of the modification. Experiments ought to be designed in such a way as to modify K without modifying k. This task

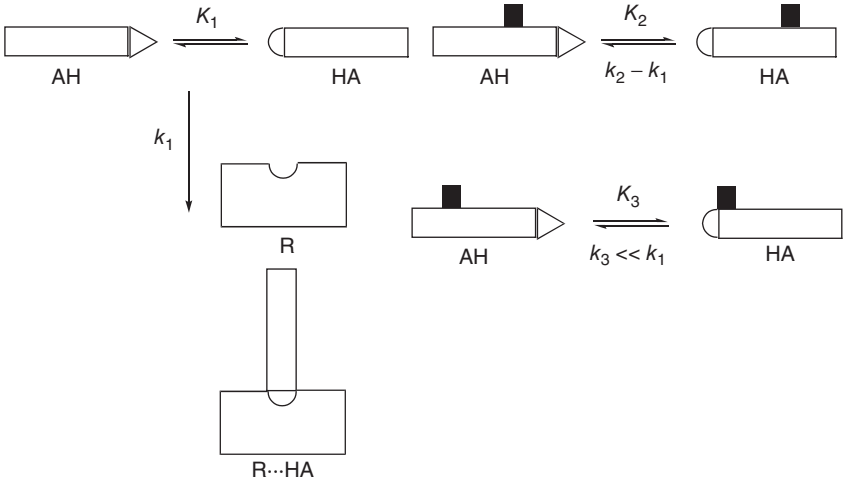

Figure 1.1 Tautomeric equilibrium disturbed by a molecular modification.

remains to be accomplished. The importance of tautomerism in biology has been emphasized in the last edition of the Encyclopedia of Genetics [44].
A very important problem that is still very difficult to solve *ab initio* is the prediction of pK_a values in aqueous solution. For some compounds, this issue is linked to tautomerism, as for instance in guanidines [45] and in NH-pyrazoles [46].

3) ***Solid state*:**
Since the *ab initio* prediction of crystal structures is still only a partly resolved problem [47], to explain why a particular tautomer is found in the solid state will require further studies. Often, the solid state tautomer corresponds to the most stable one in solution [48] but this "thermodynamic rule" only works reasonably well when the difference in energy between tautomers is large enough.
An aspect that will increase in importance is the study of tautomerism of compounds adsorbed on metallic surfaces. Two recent examples are: (i) tautomerization of 5-(4-pyridyl)-1,3,4-oxadiazole-2-thiol from thione to thiol when adsorbed on gold [49] and (ii) modification of the tautomers of azacytosines after adsorption on Au single crystal surfaces [50].

1.2
Kinetic Aspects

1.2.1
What Is Well Known

1) ***Gas phase*:**
If one accepts that only those problems that can be numerically formulated are well understood, consider then that reaction profiles are now standard outputs of computer programs.

2) ***Solution*:**
The simplest and straightforward effects of the kinetic aspects of tautomerism are the consequences they have on the use of NMR, by far the most common technique to determine equilibrium constants. If the rates are slow, a simple integration of the ^{1}H NMR spectrum will suffice. If they are fast, then interpolation methods are required. In between, low temperature studies could provide both K and k. It should be noted that the prototropic processes involving C–H bonds are slow and all the others are fast (O–H, S–H, N–H), especially the intramolecular X–H$\cdots$Y ones, such as those present in the enols of β-diketones.

3) ***Solid state*:**
Solid state proton transfer (SSPT) occurs between tautomers and, even if the initial and the final are the same (degenerate tautomerism, $K = 1$), it constitutes one of the best known kinetic processes. The loss of freedom due to the crystal structure allows for accurate kinetic models to be used, including the Car–Parrinello [51] and Bell–Limbach tunneling model [52]. This field owes much to the works of Limbach *et al.* [53, 54] and of Claramunt *et al.* [55, 56].

1.2.2
What Needs to Be Completed

1) ***Gas phase:***
   See Section ***1.2.3*** (ill known).
2) ***Solution*:**
   Problems in the relationship between tautomerism and reactivity have known to exist for a while [1] and need more quantitative studies. An aspect that should be mentioned here is the Winstein–Holness equation [57–59]. Adapted to tautomerism, it can be written as $k_{W-H} = x_1 k_{11} + x_2 k_{22}$, where x_i is the mole fraction of tautomer *i*, assuming that the equilibrium between tautomers is fast. As the less abundant tautomer is the most reactive, care should be taken when relating tautomerism and reactivity.
3) ***Solid state*:**
   See Section ***1.2.3*** (ill known).

1.2.3
What Is Ill Known

1) ***Gas phase:***
   Reliable experimental results for intermolecular proton transfer between tautomers in the ground state are sorely missing.
2) ***Solution*:**
   The window of dynamic nuclear magnetic resonance (DNMR) studies concerning reaction rates is relatively narrow, with barriers ranging from $\Delta G^{\ddagger} = 20-100\ \mathrm{kJ \cdot mol^{-1}}$ [60]. Tautomeric processes outside these limits have to be studied by other methods that are much less friendly.
3) ***Solid state*:**
   We can mention here that there are two major sources of information about tautomerism in the solid state, namely, NMR and X-ray crystallography, which have been questioned with relevance to the demand for new techniques and new goals [61]. In the incoming years, microscopies with resolutions that are similar to X-ray crystallography and femtosecond spectroscopies will become the methods of choice to obtain information about the dynamic part of tautomerism.

1.3
Conclusions

Since a deep understanding of tautomerism is dependent on the advances in theoretical chemistry, it is important to remember the problems that are, **at present**, the most difficult to calculate:

- those related to size, conformational mobility, and heavy atoms;
- those related to excited states, electronic spectra, and spin–spin coupling constants.

It is regrettable that so many publications are devoted to trivial tautomeric studies whereas only a few report interesting studies; however, it is understandable since unfortunately interest and difficulty are related.

Since all chemistry has solid quantum foundations, one cannot expect any surprises in the future in this or any other field, although many unexpected experimental results will certainly appear. The role of theoretical chemistry will increase as new methods (bear in mind the tremendous impact of Density Functional Theory (DFT) [62]) and new hardware (quantum computers [63]) will become available. Remember however, that the goal of theoretical chemistry should be "to predict." Quoting Kitaigorodskii in a lecture in 1975: "A first-rate theory predicts; a second-rate theory forbids and a third rate theory explains after the event" [64, 65].

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