THEORY OF TAUTOMERIC EQUILIBRIUM IN SOLUTION

EFFECT OF SOLVATION ON THE EQUILIBRIUM BETWEEN THE KETO AND ISOMERIC CIS AND TRANS ENOL FORMS

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During recent years we have shown that the theory of acid-base protolytic equilibrium is applicable to prototrope tautomeric equilibrium [1]. By the use of this theory we have succeeded in deriving some important quantitative relationships characterizing keto-enol tautomeric equilibrium. These calculations were based on the concept of the ionization-protolysis mechanism of tautomeric change, which has been advanced at various times and in various forms by a number of authors, particularly Pedersen [2].

The results of numerous investigations on keto-enol tautomeric equilibrium in solution indicate that it is an acid-base equilibrium of two acids— the keto and enol forms—which yield, by ionization, the same, common anions of enolate structure. Proton transfer from keto to enol and back is effected by the participation of proton-carrier molecules S, which can unite reversibly with a proton.

$$\begin{align*}
-C=O + S & \rightleftharpoons -C-O^- + H^+ S^- \rightleftharpoons -C-O^- + \text{HS}^+ \\
-C-H & \rightleftharpoons -C-H^- + \text{HS}^+
\end{align*}$$

The part of proton carrier (S) may be played by any species having an affinity for a proton. This can be solvent molecules, if they have basic properties (water, alcohols, ethers), and solvent anions (hydroxyl anions in water, acetate anions in an acetic acid solution, which are known to have strongly basic properties); this can consist also of the molecules of any bases present in the solution (pyridine, amines, etc.). Finally, in aprotic solvents, such as benzene, carbon disulfide, and hydrocarbons, the part of proton carrier (S) may be played by the molecules of the keto-enol compound themselves, to an extent depending on their ability to unite with protons. In all cases the role of the species S is the same: to remove a proton from one place in an organic molecule (for example, from the methylene group of the keto form), and then to attach the proton to another place in the anion formed (for example, to the oxygen of the enolate ion), and vice versa.

In one of the stages of tautomeric change, the process proceeds with transfer of reaction center [3]. That is to say, in the

\[\begin{align*}
-C=O & \rightleftharpoons -C-O^- \\
-C=O & \rightleftharpoons -C-O^- \rightleftharpoons -C-O^- + \text{HS}^+ \\
-C-H & \rightleftharpoons -C-H^- + \text{HS}^+
\end{align*}\]

protolysis of the keto form, the anionic charge appears not on the carbon atom from which the proton goes, but on the oxygen atom at the other end of the conjugated system H-C=C=O. Also, in the recombination of the ions with formation of the keto form:

\[\begin{align*}
\text{HS}^- & \rightleftharpoons \text{HS}^- + \text{HS}^+ \\
\text{HS}^- & \rightleftharpoons \text{HS}^- + \text{HS}^+ \\
\text{HS}^- & \rightleftharpoons \text{HS}^- + \text{HS}^+
\end{align*}\]

the proton unites not with the oxygen atom on which the anionic charge is concentrated (or almost entirely concentrated), but with the carbon atom at the other end of the conjugated system O-C=C.

Ionization of the enol form and the reverse recombination of ions in the direction of the enol form occur without transfer of reaction center: the ionic charge arises and subsequently disappears at the atom in the molecule from which the proton breaks away and to which it later returns. Protolysis of the enol form is rapid, whereas protolysis of the keto form (pseudoacid) is slow.

From the physicochemical point of view, keto-enol tautomeric equilibrium is a complex case of acid-base protolytic equilibrium in solution. It differs from ordinary acid-base equilibrium in two respects: In the first place,
there are two acids instead of one corresponding to one sort of anion, so that the anion has two different basicity constants (for addition of the proton at two different places in the anion); and, in the second place, one of the acids taking part in the equilibrium (the keto form) is a pseudoacid, which ionizes slowly. In other respects, keto-enol tautomeric equilibrium is subject to the same laws as the ionization equilibrium of the usual weak acids.

This concept of keto-enol tautomeric equilibrium is no doubt applicable also to other forms of prototropic equilibrium in substances of an acidic character. We must point out that the formation of a pseudoacid is not an essential feature of the tautomeric equilibria of acids: In lactim-lactam tautomerism, for example, both forms are true acids. We must point out also that such concepts must be applicable also to the prototropic tautomism of substances of a basic nature. In this case, proton transfer is accompanied by the formation not of a common anion, but of a common cation, which arises from both tautomeric forms as the result of the addition of a proton to each of them at different ends of the conjugated system of atoms. This occurs, for example, in amide tautomerism:

\[
\begin{align*}
-C= & N \\
-N= & H
\end{align*}
\]

It may be considered that keto-enol tautomeric changes in acid media proceed by a similar mechanism (for example, in sulfuric acid solution [4]), and that this applies in general for the acid catalysis of keto-enol changes. We consider that the laws found for keto-enol equilibrium are of a general character, and may be extended, with some modifications, to other examples of tautomerism.

As we have shown, the application of the theory of acid-base protolytic equilibrium to the ternary buffer system:

\[
KH + S \rightarrow E^- + HS^- \rightarrow EH + S,
\]

(in which KH represents the keto form, and EH the enol form) results (for dilute solutions) in a simple relationship between the tautomeric equilibrium constant \( K_{TS} \) and the ionization or protolysis constants of the keto and enol forms, treated as acids:

\[
K_{TS} = \frac{[EH]}{[KH]} = \frac{K_{KS}}{K_{ES}} = \frac{K^*_{KS}}{K^*_{ES}} = \frac{K_K}{K_E} f_{KS} f_{ES}.
\]

\([EH] \text{ and } [KH] \text{ are the concentrations of the tautomers;} \ K_{KS} \text{ and } K_{ES} \text{ are the ionization constants of the keto and enol forms;} \ K_K \text{ and } K_E \text{ are the corresponding constants for protolysis by the base } S; \ K_K \text{ and } K_E \text{ are thermodynamic acidity constants; and } f_{KS} \text{ and } f_{ES} \text{ are activity coefficients.}\]

The tautomeric equilibrium constant is equal to the ratio of the ionization constants of the keto and enol forms in the given solvent (and also to the ratio of the protolysis constants): it is equal also to the ratio of the thermodynamic acidity constants of the keto and enol forms, multiplied by the ratio of the activity coefficients. The ratio of the thermodynamic acidity constants does not depend on the nature of the solvent: it may be termed the "thermodynamic constant" of tautomeric equilibrium \( K_t \):

\[
K_t = \frac{K_K}{K_E}.
\]

It characterizes the "enolizability" of the tautomeric compound, quite apart from any effect due to the solvent. The higher the acidity constant of the keto form and the lower the acidity constant of the enol form, the higher the "enolizability" of the given tautomeric compound.

* The ratio \( f_{KS} / f_{ES} \) expresses the effect of the solvent on the keto-enol tautomeric equilibrium, i.e., its "enolizing power". Here the most important factor is the nature of the solvation of the keto and enol forms by the given solvent. The higher the solvating effect of the solvent on the enol form (the undissociated molecule), the lower its activity coefficient and the greater the enolization in the given solvent; and vice versa.

In each case the position of equilibrium will be determined by both factors: the "enolizability" of the tautomeric compound, given by the value of \( K_t \), and the "enolizing power" of the solvent \( f_{KS} / f_{ES} \), which depends on the relative degree of solvation of the forms. The position of tautomeric equilibrium is always found to be displaced in the direction of the form that is the less acidic in the given medium.

* Activities being related to a standard state that is the same for all solvents.