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The effects of tautomerism on the nature of molecules in the solid state

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Abstract Tautomerism is a phenomenon well know to most chemists but frequently forgotten when chemistry leaves the bench and enters the computational realm. Through the examination of several examples from the crystallographic literature it can be clearly demonstrated that the tautomeric state of a molecules can strongly affect its nature.

Keywords Crystallography · Tautomerism

Introduction

Modern computational tools rely on an accurate molecular model or at least a chemical structure. In most, if not all of these, the molecule may be treated with varying degrees of conformational flexibility but in all of them the connectivity is fixed. Arguably it is not practical to do otherwise. Few if any chemists, however, are unaware of the fluxional nature of the bonding in many molecules. Yet in many cases tautomerization and its effects on the nature of a molecule are neglected. It falls on the chemist using these techniques to keep in mind that when tautomerization is possible, the multiple tautomers are each present to some degree and can be accessed to the chemists' advantage or neglected at their risk.

A number of examples in which tautomerization affects the fundamental character of a molecule can easily be found by a survey of crystal structures containing well known tautomeric moieties [1]. Several of these systems and the effects of tautomerization on them will be discussed.

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4-Hydroxypyridine

4-hydroxypyridine is a well know fluxional system occurring in the two tautomers shown in Fig. 1. The crystallographic literature contains numerous examples of both tautomers, in a few cases both occurring in the same material. Highlighted here, however, is a 4-pyridone containing compound selected for the stark effect that tautomerism has on its molecular character. 3,6,9,12,15-Pentaoxa-21-azabicyclo(15.3.1)heneicosa-17,20-dien-19(21H)-one (compound A) is a crown-ether-like compound shown in Fig. 2.

The pyridone form can be seen in Fig. 3 [2]. In this form, the presence of the amine hydrogen atom in the crown ether-like molecules has the rather strong effect of causing what might be expected to be a macrocyclic cavity to collapse. This is in spite of the fact that a possible guest molecule is present in the form of a water molecule. In many crystal structures of the analogous 18-crown-6, a water molecule is found housed in the macrocycle's cavity. More similarly still is the compound 19-Hydroxy-3,6,9,12,15-pentaoxa-21-azabicyclo(15.3.1)henicosa-1(21),17,19-triene-2,16-dione (compound B shown in Fig. 2) which differs from compound A only in that the carbon atoms adjacent to the six-membered ring are carbonyls rather than aliphatic carbons. Compound B, like 18-crown-6 is shown, in its hydrate form, to form a macrocyclic cavity and host its water of hydration in this cavity [3]. This is illustrated in Fig. 6. It is not unreasonable, therefore, to think that even in the presence of the pyridone proton a macrocyclic structure could exist and accommodate the water molecules or alternately, that compound A could assume the hydroxypyridine configuration. In several other structures, this is exactly what occurs [2, 4]. These can be seen in Figs. 4 and 5. It can be inferred then that in order to take advantage of the macrocyclic cavity,

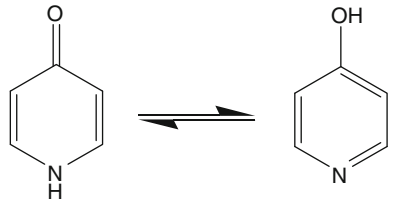

Fig. 1 4-pyridone/4-Hydroxypyridine tautometic system

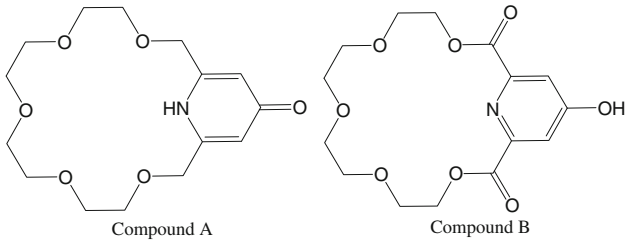

Fig. 2 Compound A and B

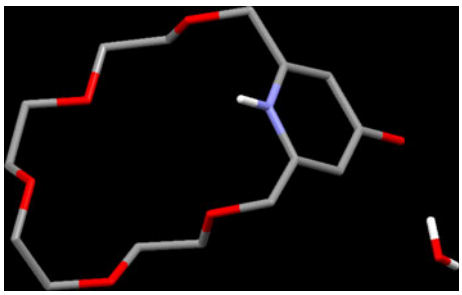

Fig. 3 Compound A mono-hydrate with a collapsed macrocyclic cavity

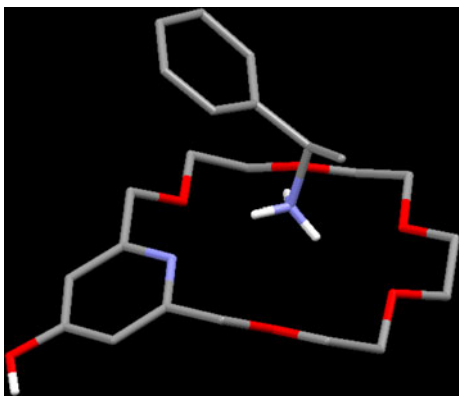

Fig. 4 Compound A in a macrocyclic configuration hosting a hydrogen bonding guest

sufficient energetic advantage must exist to overcome the inhibition to form the hydroxypyridine configuration. It can also be surmised that the incorporation of a water molecule doesn't provide the necessary energetic advantage (Fig. 6).

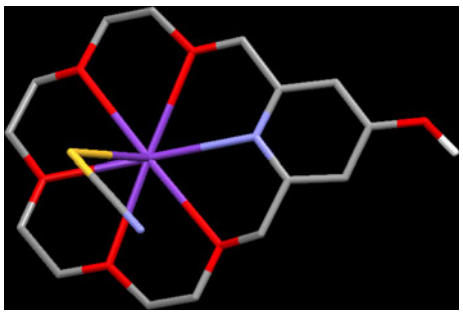

Fig. 5 Compound A in a macrocyclic configuration hosting a metallic guest

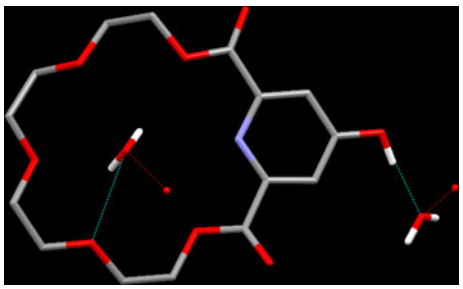

Fig. 6 Compound B in a macrocyclic configuration hosting a water molecule

Sulfonamides

Sulfonamides are a structural class of compounds broadly represented in the pharmaceutical field, not least prominently in the sulfa drug class of antibiotics. It is strongly demonstrated in the literature, however, that to refer to them as sulfonamides at all is somewhat misleading due to the fact that a sulfonimide tautomer, as shown in Fig. 7, is not only represented in the crystallographic literature but, with approximately 25% of structure in the sulfonimide form rather than the namesake tautomer, strongly so.

These two tautomers differ strongly in their potential hydrogen bonding motifs. One of the most common hydrogen bonding motifs seen in this class of compounds is a dimer in which the sulfonamide nitrogen donates a hydrogen bond to the pyridine nitrogen [5]. This is seen in many cases such as refcode INIPOK. This motif is also possible in the sulfonimide form [6] as shown in refcode EBIDAV. A generalized illustration of each of these dimers can be seen in Fig. 8.

There is, however, a second hydrogen bonding motif that is seen in the sulfonimide which is not possible in the sulfonamide. This motif consists of an infinite chain as is shown in Fig. 9. This motif is typified by refcode EBICEY [6].

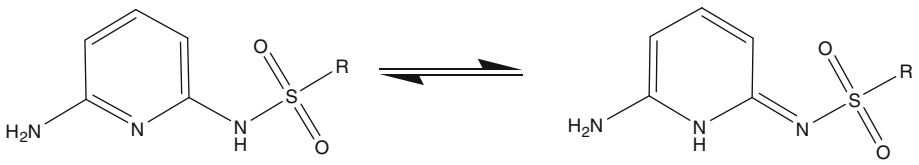

Fig. 7 Tautomerization in sulfonamides

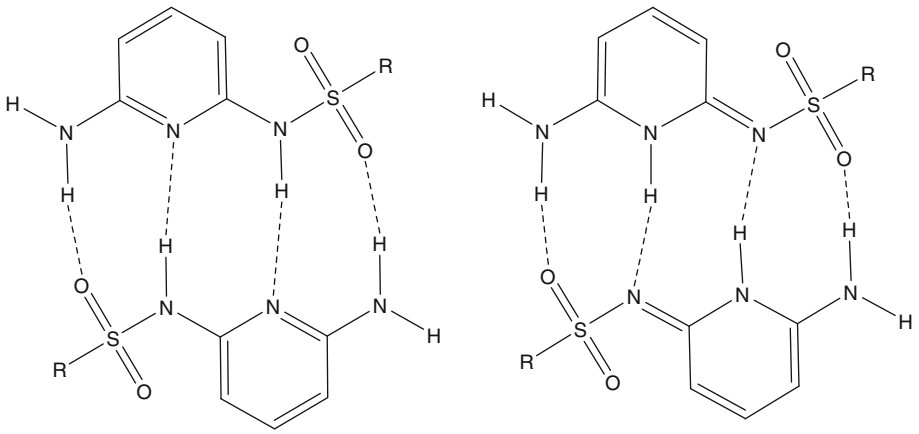

Fig. 8 Dimer hydrogen bonding motif in the sulfonamide and sulfonimide tautomers

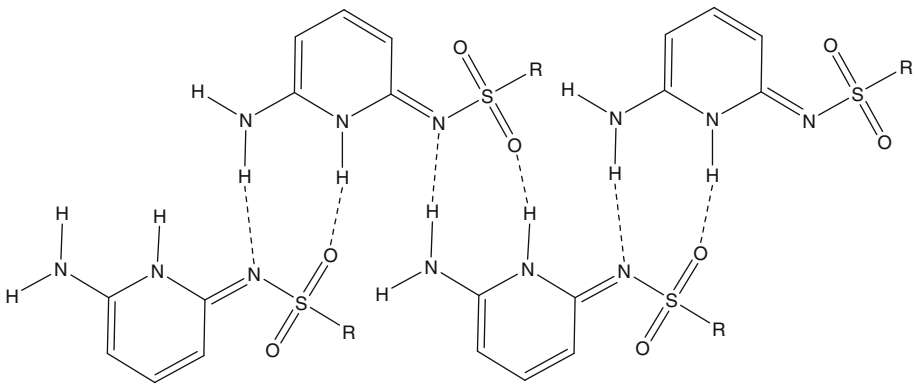

Fig. 9 Sulfonimide specific hydrogen bonding motif

Discussion

The two examples outlined above are illustrative of the importance of considering tautomerism to the thorough understanding of a molecular system.

In compound A we have an example of a molecule which does or does not contain a macrocyclic cavity, depending on the environment and what other species are present in solution. In the related compound B no such adaptive character is exhibited. A macrocyclic cavity is always present in compound B but it is also true that there is no crystallographic example of compound B in the pyridone configuration with a protonated nitrogen atom. It may be true that the conditions for the protonated pyridone tautomer to form may just not have been met or it may be that the differences between compound A and compound B make it too energetically unfavorable for it to exist. What is unquestionably true is that in the absence of sufficient structural data the adaptive nature of compound A would remain undetected. That adaptive nature's link to tautomerism in the molecule would likewise be unobserved.

The sulfonamide system discussed illustrates that even in homogenous system, where only homo-synthons exist, multiple homo-synthons are seen and one of the two homo-synthons is only accessible to one of the two tautomeric configurations. This has implications in any endeavor in which the hydrogen bonding of a molecule is a consideration, from crystal engineering to the assessment of binding to a protein. The hydrogen bonding pattern in the sulfonamide tautomer might be unsuited to a particular protein binding site but the sulfonimide might be ideal or vice versa. If both tautomers are not considered, important opportunities could be missed. Similarly, in the field of crystal engineering, when considering possible hetero-molecular synthons for the selection, different possibilities exist for each of the two tautomers. To neglect one of the

two eliminates half of the possibilities before a single experiment is conducted. Possibilities that at the very least would have added to the body of structural knowledge and at their best could have opened up new avenues of study or produced a useful new material.

In general neglecting to include potential tautomers in three dimensional models limits the usefulness of the models. The selected examples clearly show that the nature of a molecule can be strongly affected by its tautomeric state. In such cases, the omission of a model for the alternate tautomer leads to an incomplete understanding of the molecule. When an incomplete model is used in molecular modeling; such as the calculation of surface binding for the purpose of habit modification, polymorph prediction, or protein binding; only an incomplete evaluation of these processes can be expected as an outcome. Even simpler model based calculations such as polar surface area or dipole moment would still be under evaluated without the inclusion of tautomers. Lastly, it should be noted that with the increased, now ubiquitous, use of structure based prediction of chemical properties, such as pKa or CLogP, an overly simplified model of a dynamic tautomeric system inevitably leads to poorly predicted properties.

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