A Density Functional Theoretical Study of the Influence of Cavities and Water Molecules on Tautomerism: the Case of Pyridones and 1,2,4-Triazoles Linked to crown Ethers and Esters

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Dedicated to Professor Jerald S. Bradshaw

The tautomerism of pyridones and 1,2,4-triazoles related to two crown ethers and two crown esters derived from these heterocycles was studied theoretically. For the four macrocycles, Bradshaw identified a single tautomer by X-ray crystallography. To rationalize these findings, a series of calculations from simple models to crown derivatives have been carried out. The most interesting case concerns the observation, for the first time, of a 4*H*-1,2,4-triazole tautomer. To explain this result it was necessary to calculate the whole crown ester plus a caged water molecule was necessary.

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Tautomerism is today well understood based on some useful empirical generalizations [1-3] as well as on theoretical calculations, specially taking into account that with the advents of density functional techniques, computations of energies of molecules of medium size are within the reach of any organic chemist. The possibility of using these methods to approach tautomeric problems is open to all experimentalists even if tautomerism is a particularly difficult case for computational methods [4,5].

We decided to study the effect of an intramolecularly linked crown-ether or ester on the tautomerism of two paradigmatic cases [1]: i) the lactim-lactam equilibrium of 4-hydroxypyridine, and ii) the annular tautomerism of 1,2,4-triazole. We selected these cases because, according to Bradshaw, the equilibrium is reversed depending on the nature of the crown, ether or ester. In total, four molecules were considered, and the two possible tautomers for each molecule are shown in Figure 1. Bradshaw obtained crystals of these molecules containing only one tautomer in each case; these are: **1a** (CSD refcode [6], DABWUY10) [7], **2b** (CSD refcode, DABXAF10) [8], **3a** (CSD refcode, FEVPAX) [9], **4b** (R = CH_3, CSD refcode, DEGNIM) [10]. Three of these compounds crystallize with a water molecule: **1a**•H_2O, **2b**•H_2O and **4b**•H_2O; the water molecule is inside the cavity in the case of **4b**, and outside in the cases of **1a** and **2b**.

Computational Details.

Calculations were carried out at the B3LYP/6-31G* level of theory [11,12] with the Gaussian-98 program [13]. This level has been successfully used to study the tautomerism of 4-pyridone *vs*. 4-hydroxypyridine [14]. The minimum nature of the structures has been confirmed by frequency calculations (no imaginary frequencies).

Results and Discussion.

We will describe our results in a four step ascending order: i) the parent compounds; ii) the effect of ether and ester substituents; iii) the effect of crowns; iv) the effect of water molecules of crystallization.

i) The Parent Compounds.

a) *The tautomerism of 4-hydroxypyridine/4-pyridone*. The pioneering work of Beak and Katritzky [15,16] (see [17] for a recent paper) have established that of the two tautomers of pyridone, the hydroxy form **5b** is the most

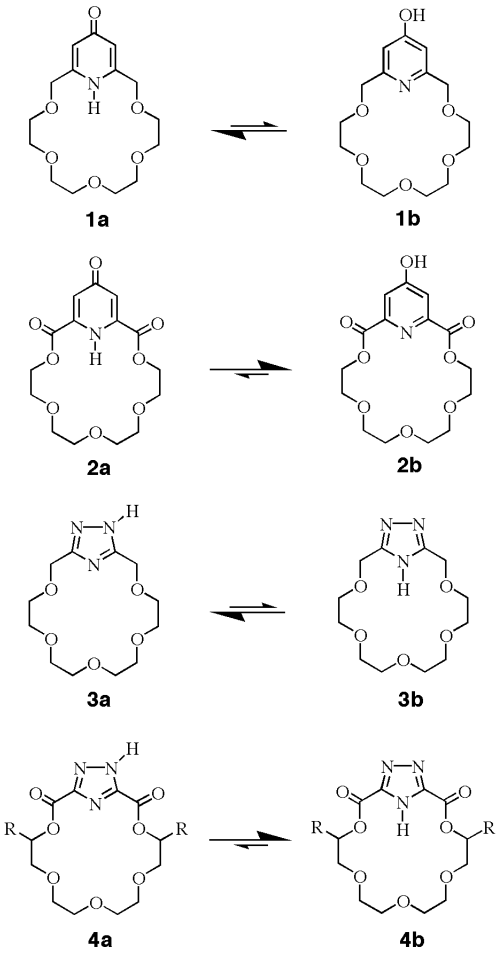
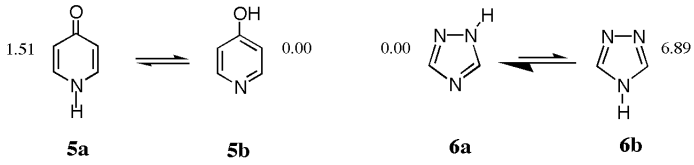


Figure 1. The four tautomeric equilibria.

stable in the gas phase, while the oxo one becomes the most stable in polar solvents, specially in water, as well as in the solid state. In the gas phase, the difference in energy was estimated in 1976 to be more than 2 kcal mol^{-1} (K_T < 0.1) in favor of **5b** [15]. The only recent experimental study of the tautomerism of **5** in the gas phase is due to Buyl, Smets, Maes and Adamowicz [18]; the FT-IR spectrum in Ar matrices shows no trace of **5a**, thus, K_T should be < 0.01 (> 2.7 kcal mol^{-1}).

Computations of the equilibrium **5a**/**5b** by Hillier [19] and by Sordo and Fraga [20] predict **5b** to be more stable than **5a** in the gas phase. At the B3LYP/aug-cc-pVDZ//B3LYP/6-31G* level, ΔE = 2.42 kcal mol^{-1} [14] and at the MP2/6-31++G**//6-31++G** level, ΔE = 5.18 kcal mol^{-1} [18]. The most recent and comprehensive study is due to Reimers, Hall and Hush [21], who use single-point energy calculations [SCF, MP2, MP4, QCISD, CCSD, CCSD(T), HCTH, B3LYP] with a series of basis sets (3-21G, cc-pVDZ, aug-cc-pVDZ, cc-pVTZ). These authors conclude, that there is no relationship between ΔE and the quality of the calculation and that the values of ΔE are always positive (save for the B3LYP/3-21G calculation) and comprised between 0.6 and 5.5 kcal mol^{-1}. Their best estimation is 3.2 kcal mol^{-1} in favor of **5b** [21].



b) *The tautomerism 1H-1,2,4-triazole/4H-1,2,4-triazole*. The case of 1,2,4-triazole is simpler because is it highly biased in favor of the 1*H*-tautomer **6a**. All theoretical calculations [22-24] favored the 1*H*-1,2,4-tautomer **6a** over the 4*H* **6b** by about 7 kcal mol^{-1} [24], in agreement with all experimental results [1-3]. Although in very polar solvents about up to 5% of **6b** may be present [3]. In 2,3-diazaporphyrins, the tautomer containing a 4*H*-triazole sub-unit is so disfavored that a non-aromatic structure is preferred for the triazole [25]. Reciprocally, Bradshaw's result concerning **4b** is the most surprising of the four examples represented in Figure 1.

At the B3LYP/6-31G* level we obtained a difference of 1.51 kcal mol^{-1} in favor of the 4-hydroxypyridine **5b** and a difference of 6.89 kcal mol^{-1} in favor of the 4*H*-1,2,4-triazole tautomer **6a**. Therefore, in a first approximation, **2b** and **3a** are "normal" tautomers and **1a** and, mainly, **4b** are "abnormal" tautomers.

ii) The Effect of Ether and Ester Substituents.

Owing to the size and molecular flexibility of the crown ethers and esters and the size of molecules represented in Figure 1, we decided to begin the computational approach studying the model compounds, **7a** to **10b**, represented in Figure 2.

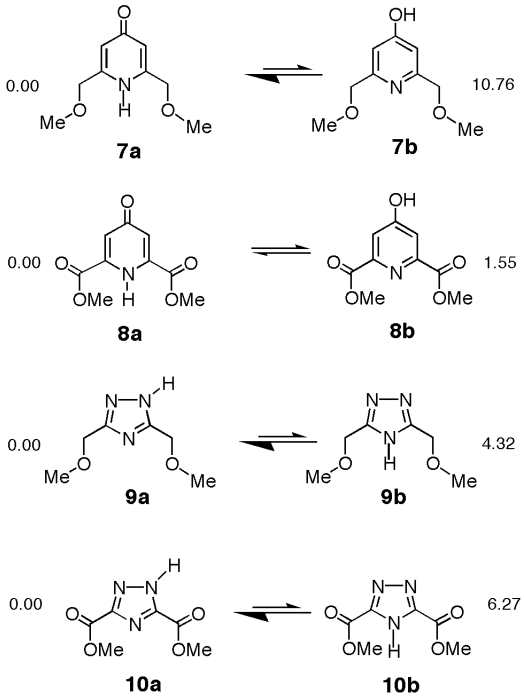


Figure 2. The equilibria involving model compounds with the differences in energy in kcal mol^{-1}.

In Table 1 are gathered the results obtained and in Figure 2 the differences in energy in kcal mol^{-1} (the same that has been done for the parent compounds **5a** to **6b**). Although we have calculated the ZPE corrections, we will use the E_{rel} without ZPE because in one case, compound **7b**, the structure is not a minimum but a fourth order transition state owing to the tendency of the methoxy substituents to adopt a conformation different from that in the crown **1b**. In any case, the difference between E_{rel} and E_{rel}+ZPE is small and can be considered as a minor perturbation.

Concerning pyridine-crown ethers **1**, in the parent compound **5**, the hydroxypyridine tautomer is more stable than the pyridone (remember that the value is very dependent on the method [21]); the presence of two methoxymethyl substituents at positions 2 and 6 strongly shifts the equilibrium towards the pyridone tautomer **7a** (about 11 kcal mol^{-1}). This agrees with the predominance of tautomer **1a**, specially taking into account the higher dipole moment of **7a** compared with **7b**, which should favor the pyridone in polar solvents and in the solid state.

Concerning pyridine-crown esters **2**, the two ester substituents present in model **8** produce an effect similar but much smaller: tautomer **8a** is slightly favored over **8b**. Since our calculations underestimate the stability of **5b**,

Table 1

B3LYP/6-31G* Calculations of Compounds **5**-**12** (Absolute Values in Hartrees, ZPE and Relative Values [Most Stable Tautomer in Brackets] in kcal mol^{-1}, Dipole Moments in D)

Compound	Tautomer **a**	Tautomer **b**	E_{rel}	ZPE (**a**)	ZPE (**b**)	E_{rel} + ZPE	μ(**a**)	μ(**b**)
Pyridines								
5	-323.50176	-323.50417	1.51 (**b**)	58.79	58.55	1.76 (**b**)	6.68	2.74
7	-631.16245	-631.14529	-10.76 (**a**)	171.10	[a]	[a]	7.62	2.57
8	-779.25782	-779.25534	-1.55 (**a**)	112.66	112.35	-4.09 (**a**)	8.72	1.41
Triazoles								
6	-242.24927	-242.23830	-6.89 (**a**)	37.63	37.08	-6.34 (**a**)	2.87	5.62
9	-549.91646	-549.90958	-4.32 (**a**)	114.47	114.24	-4.09 (**a**)	3.01	5.07
10	-697.99792	-697.98793	-6.27 (**a**)	91.56	91.06	-5.77 (**a**)	3.34	8.37

[a] The corresponding structure is not a minimum but a four order saddle point.

Table 2

B3LYP/6-31G* Calculations of Pyridone Crown Ether **1** and Triazole Crown Ester **4** (Absolute Values in Hartrees, Relative Values in kcal mol^{-1} [Most Stable Tautomer in Parentheses], Dipole Moments in D)

Compound	Tautomer **a**	Tautomer **b**	E_{rel}	μ(**a**)	μ(**b**)
1	-1091.46565	-1091.45201	-8.56 (**a**)	7.50	3.90
2	-1239.55409	-1239.54628	-4.90 (**a**)	9.96	2.38
4	-1158.28373	-1158.28245	-0.81 (**a**)	4.37	10.37
4•H_2O	-1234.71657	-1234.72601	5.93 (**b**)	5.52	13.20

probably the same happens with **8b** and the structure **2b** continues to be "normal".

If we turn now to triazole derivatives, tautomer **3a** is expected, on general grounds, to be the most stable. The difference, with regard to **6a**, is decreased by the methoxymethyl groups, still **9a** is more stable than **9b**. The surprising stability of **4b** is not explained by compound **10**, which behaves almost identically to **6**.

In conclusion, concerning the balanced pyridone/ hydroxypyridine equilibrium, the case of the stability of the crown ether **1a** is conveniently explained by the study of the model compound **7**. On the other hand, the stability of the crown esters **2b** is not conveniently reproduced by the model. The case of triazoles is very different because the equilibrium of the parent compound is strongly biased in favor of the 1*H*-tautomer **6a**. The presence of **3a** in the crystal does not require a model compound study even though **9** reproduced the experimental observation correctly. Finally, the isolation of structure **4b** (R = CH_3) in the solid state continues to remain unexplained after this first approach.

iii) The Effect of Crowns.

In the case of pyridones, the calculations reported in Table 2, confirm the greater stability of **1a** compared with **1b**. In the case of the crown-ester, the difference of 1.55 kcal mol^{-1} (**8a**/**8b**) is increased to 4.90 kcal mol^{-1} in contradiction with the experiment (structure **2b**).

In the case of triazoles, the problem is reduced to explain the sense of "abnormal" equilibria **4a**/**4b**,which was studied for R = H although the experimental result was obtained for R = CH_3. The result is reported in Table 2.

For compound **4**, the crown ester produces an extraordinary stabilization of tautomer 4*H*, which is now only 0.8 kcal mol^{-1} less stable than tautomer 1*H*. Moreover, the **b** tautomer has a much higher dipole moment.

iv) The Effect of Water Molecules of Crystallization.

There are two ways of including the effect of water solvation on the tautomeric equilibrium. The first one is to study the effect of water as a general solvent; this approach has been explored by Gao in a series of papers, who found that the gas phase preference of the hydroxy tautomer **5b** is dramatically reversed in water in favor of the oxo form **5a** by -3.7 kcal mol^{-1} [26]. More recent papers have confirmed these findings [14,21]. The other possibility is to study the supermolecules **5**•H_2O. Maes *et al*. found five different positions of the water molecule that are minima of the potential hypersurface (Figure 3). Their SCF/6-31++G** calculations lead to the conclusion that the difference in favor of hydroxypyridine **5b** remains unaltered

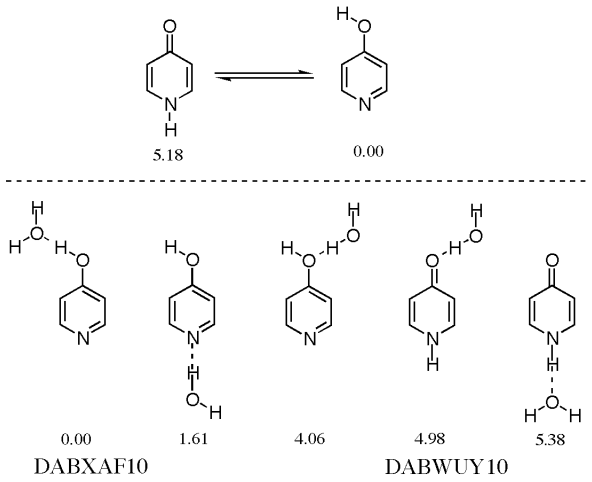


Figure 3. A summary of the results from ref. [18] with energy differences in kcal mol^{-1}.

[18]. The situations found by Bradshaw [7,8] for **1a** (DABWUY10) and **2b** (DABXAF10) have the water molecule outside the crown cavity.

Our position concerning the role of the water molecules on the structures described by Bradshaw is as follows. The enthalpic and entropic reasons why a compound crystallizes with a solvent molecule is very complex [27] and falls outside our present work. A study similar to that of Maas for compounds **1** and **2** with at least five positions for the water molecules would be interesting for gas phase cluster. Therefore, we decided to leave outside the case of crown ether **3** which crystallizes without water and also the case of pyridine derivatives **1** and **2** because in both cases the water is outside the cavity and according to reference [14] it has no effect on the tautomerism.

A calculation has been carried out on the supermolecules **4a**•H_2O (inside) and **4b**•H_2O (outside) (R = H). In the case of **4a**, the water molecule accepts an HB from the N(H)1 of the triazole and acts as HB donor towards the proximal carbonyl group, while in **4b**, the water molecule occupies the same position as in the crystal [10] (Figure 4, note that DEGNIN corresponds to R = CH_3 and the calculation to R = H). Furthermore, the geometry of **4a**•H_2O (R = CH_3) reported in reference 10, differs from that of the Cambridge Structural Data Base [6]: we have used in Figure 4 the CSD Base data.

The inclusion of a water molecule completely shifted the equilibrium towards tautomer **4b**, in complete agreement with Bradshaw's observation [10]. Finally, since the molecular structure of compound **4b** (R = CH_3, a hydrate, DEGNIM) [10] has been determined by X-ray crystallography, it is possible to compare its geometry with those of the corresponding calculated tautomers **4b** and **4b**•H_2O.

The overall conformation of the X-ray structure of **4b**•H_2O (R = CH_3, DEGNIM) is more planar than the corresponding calculated one (**4b**•H_2O, R = H) probably due to the packing effects. Concerning the caged water molecule, the shortest HB distance, N-H···O, is almost similar in the experimental and calculated structures (1.634 and 1.661 Å respectively) while the other two HB, O-H···O, are similar in the calculated system (average 2.06 Å, Figure 4) but shorter in the crystal (average 2.00 Å).

Conclusion.

To summarize the results of Figure 1, i) the crown ether stabilized **1a** which is the tautomer isolated by Bradshaw; ii) **2b** is the normal hydroxypyridine tautomer, therefore it is not a surprise that it was found in the crystal although our calculations do not reproduce this result; iii) the same hap-

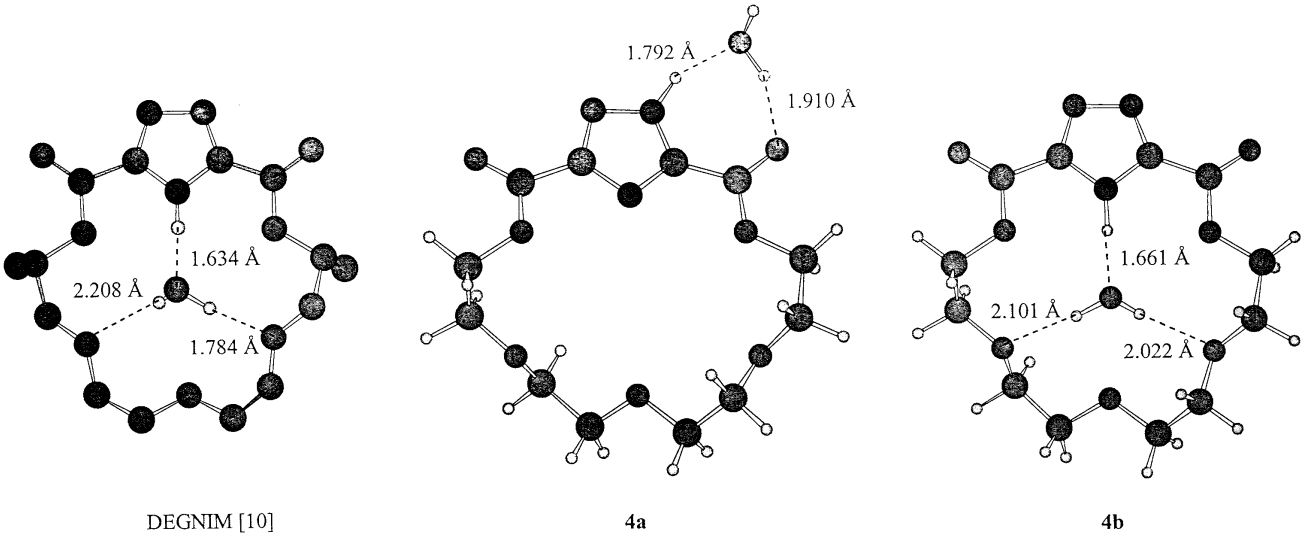


Figure 4. Comparison of the geometries of triazole-crown ester **4**.

pens with **3a** which is the normal 1*H*-triazole tautomer. Finally, to justify why **4a** is the only known example of a 4*H*-triazole tautomer, it is necessary to link it to a crown ester and to add a water molecule within it. It is not reasonable to expect a better fit of experiments and calculations taking into account that crystal packing effects are not considered in our approach, although they are determinant.

One last remark, we have often pointed out that the tautomer found in the solid state corresponds generally to the most abundant tautomer in solution (polar solvents) [1-3]. Consequently, the present discussion is probably relevant for solution studies of tautomerism.

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