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Theoretical study on the solvent influence on 1,2,3-triazole tautomeric equilibrium. A comparison of incremental microsolvation and continuum solvation model approaches

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The effect of solvent on the 1,2,3-triazole tautomeric equilibrium was studied by calculating Gibbs free energies of tautomerization in the gas-phase and in water solution at MP2/aug-cc-pVDZ, B3LYP/6-311++G(d,p) and wB97XD/6-311++G(d,p) levels of theory. Three models of solvation were investigated: (1) gas-phase incremental microsolvation with explicit water molecules leading to (triazole)$(H_2O)_n$ clusters where n=1,2,3,4,5; (2) continuum solvation via PCM, SMD and CPCM methodologies applied to an isolated triazole molecule; (3) combination of models (1) and (2) where the system was treated by both: incremental microsolvation and continuum (PCM) approach. Model (3) gives very good agreement with experimental results when the number of water molecules in the (triazole)$(H_2O)_n$ cluster is equal to 5. However in the case of 3 and 4 water molecules, the results are much less reliable. The reasons behind this behaviour are analyzed and the importance of taking into account the proper number of water molecules in a microsolvation study is discussed.

1. Introduction

1,2,3-Triazoles form an important class of heterocycles with rich chemistry and many applications in medicine, agriculture and industry.[1,2] Their varied biological activity enables their use as antifungal,[3] antibacterial,[4–7] antivirial,[8,9] analgesic,[10] antiallergic,[11] antiplatelet,[12] anticonvulsant,[13] antitumour[14] and sun-protective[15] medicines. Due to their complexation strength they have found application as corrosion inhibitors, especially for copper.[16] From a structural point of view, the presence of both pyrrole-like and pyridine-like nitrogen atoms in the triazole ring enables prototropic tautomerism.[17] The parent 1,2,3-triazole molecule can exist in two forms, which interconvert via proton transfer between the two adjacent nitrogen atoms[18,19] (Fig. 1).

Quantitative estimation of the tautomers relative ratio is an important topic, as different tautomers can have different chemical and biological activities.[13] In the following paragraphs for the sake of brevity, ΔE_T and ΔG_T symbols will be used for the energy and Gibbs free energy of tautomerization. These quantities are obtained by subtracting the appropriate physical quantity for the 2H tautomer from the 1H tautomer. The energetic difference between these two forms depends on intra- and inter-molecular factors. As was pointed out by Elguero et al.[20] in the gas-phase, the difference in stability of the two tautomers is mainly related to the so-called α-effect[21]—the repulsion of lone pairs belonging to two adjacent nitrogen atoms. This effect is present only in the 1H tautomer and leads to its significant destabilization. In solution however the situation is more complex. As the less stable 1H form possesses a much larger dipole moment: 4.38 D (2H has only 0.218 D)[22] it can be expected that in a polar solvent the energy difference between tautomers will be lowered. But by how much? Over the last 25 years tautomeric equilibria of 1,2,3-triazole has been the subject of numerous experimental and computational studies, but the energetics obtained by various authors differ, especially in the case of solvation. Results obtained by various authors are gathered in Table 1.

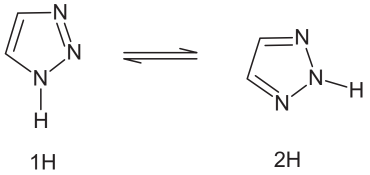

Fig. 1. Tautomeric forms of 1,2,3-triazole.

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Table 1
Author and paper reference number, methodology (experimental or theoretical) and tautomerization energy (ΔE_T) or Gibbs free energy (ΔG_T) of 1,2,3-triazole for gas-phase and water solution

Author[Ref.]	Methodology	Tautomerization energy (ΔE_T) or Gibbs free energy (ΔG_T) [kcal/mol]	
		Gas-phase	Water solution
Begtrup[22]	Microwave spectroscopy	$\Delta G_T=4.1$	
Albert[23]	Acidity and basicity values		$\Delta G_T=0.48$
Catalan[24]	HF/6-31G*//HF/6-31G	$\Delta E_T=4.7$	
Tomas[25]	HF/6-31G*	$\Delta E_T=4.9$	
Cox[26]	MP2/6-31G(d,p)//MP2/3-21G	$\Delta E_T(+\mathrm{ZPE})=3.54$	
	Molecular dynamics simulation		$\Delta G_T=1.34$
	Reaction Field Continuum solvation Model		$\Delta G_T=-1.55$
Törnkvist[27]	MP2/6-31G(d)	$\Delta E_T=5.0$	
Abboud[28]	B3LYP/6-31G(d)	$\Delta G_T=4.2$	
Murdock[29]	Monte Carlo simulation	$\Delta G_T=5.50$	$\Delta G_T=-1.62$
Nagy[30]	Monte Carlo simulation		$\Delta G_T=-1.30$
	MP2/6-31G(d)//B3LYP/6-31G(d)+PCM		$\Delta G_T=0.20$
	B3LYP/6-31G(d)+PCM		$\Delta G_T=0.37$
Ozimiński[31]	CCSD(T)/6-311++G**//B3PW91/6-311++G**	$\Delta G_T=3.95$	
Jiménez[32]	B3LYP/6-311++G(d,p)	$\Delta G_T=4.17$	
	CBS-QB3	$\Delta G_T=3.88$	
	CBS-4M	$\Delta G_T=3.39$	
Balabin[33]	focal point analysis CCSD(T)/CBS//MP2/aug-cc-pVTZ	$\Delta E_T=3.98$	
Dabbagh[34]	B3LYP/6-311++G(d,p)	$\Delta G_T=4.16$	$\Delta G_T=0.47$

First, let us look at experimental results. Begtrup et al.[22] studied triazole tautomerism in the gas-phase by means of microwave spectroscopy and obtained a relative ratio of 1H to 2H tautomers of 1:1000, which corresponds to $\Delta G_T=4.1$ kcal/mol. On the other hand Albert and Taylor[23] using acidity and basicity values of various forms of 1,2,3-triazole, estimated the 1H to 2H tautomer ratio in water solution as 1:2 with $\Delta G_T=0.48$ kcal/mol. The authors argue that the main reason for decreasing the tautomerization energy in a highly polar solvent is the lowering of the α-effect caused by the creation of hydrogen bonds with water. These two experimental values will serve in this study as a reference. Next, let us compare various computational estimations. Early theoretical results often suffered from inaccurate methodology and insufficient basis sets, as shown by Catalan et al.[24] who studied basis set effect on the gas-phase tautomerization energy by means of the Hartree–Fock method. Their HF/6-31G*//HF/6-31G calculations yielded $\Delta E_T=4.7$ kcal/mol in good agreement with experimental data. Similarly $\Delta E_T=4.9$ kcal/mol was found at the HF/6-31G* level by Tomas et al.[25] At the ab initio correlated MP2/6-31G(d,p)//MP2/3-21G level, Cox et al.[26] obtained $\Delta E_T(+\mathrm{ZPE})$ equal to 3.54 kcal/mol, a result, which includes the zero point energy (ZPE) correction. That work was the first attempt to calculate the solvation effect on the 1,2,3-triazole tautomerization energy. The authors used molecular dynamics simulation and obtained $\Delta G_T=1.34$ kcal/mol. Additionally simple RFCM (reaction field continuum solvation model) calculations were also performed for comparison, which resulted, however, in larger stability of the 1H tautomer in aqueous solution ($\Delta G_T=-1.55$ kcal/mol), and may be an illustration of the imperfection of such a simplified model. MP2 model chemistry was employed also by Tornkvist et al. who obtained at the MP2/6-31G(d) level the energy value $\Delta E_T=5.0$ kcal/mol.[27] The first density functional theory (DFT) calculation was performed by Abboud et al.[28] who obtained $\Delta G_T=4.2$ kcal/mol at the B3LYP/6-31G(d) level in the gas-phase, which is very close to the experimental value. Regarding the energy difference in solution, the authors used a reasoning similar to that of Albert et al.[23] but also point out that using a different value of a parameter used in calculation of K_T in solvation can lead to a different result $\Delta G_T=2.4$ kcal/mol, which is very different from the result obtained by Albert et al. The authors concluded that the reduction of the predominance of the 2H form in water solution was due to a much larger dipole moment of the 1H tautomer. Other methodology was employed by Murdock et al.[29] who performed a Monte Carlo simulation and obtained $\Delta G_T=5.50$ kcal/mol for the gas-phase, but $\Delta G_T=-1.62$ kcal/mol for the aqueous solution, thus a result, which favours the 1H tautomer in disagreement with the experimental findings. From these results it is obvious that obtaining a reliable value for ΔG_T in aqueous solution is not a simple task. Monte Carlo simulation was also performed by Nagy et al.[30] with $\Delta G_T=-1.30$ kcal/mol in aqueous solution, a result similar to that of Murdock et al. But at the IEF-PCM level, the relative stability of both tautomers agrees well with experimental results with $\Delta G_T=0.20$ kcal/mol for MP2/6-31G(d)//B3LYP/6-31G(d) and $\Delta G_T=0.37$ kcal/mol for B3LYP/6-31G(d) calculations. Our previous high-level ab initio CCSD(T)/6-311++G**//B3PW91/6-311++G** results[31] gave $\Delta E_T=4.90$ kcal/mol and $\Delta G_T=3.95$ kcal/mol for the gas-phase calculations. Jiménez et al. performed B3LYP/6-311++G(d,p) calculations,[32] which resulted in $\Delta G_T=4.17$ kcal/mol in even better agreement with the experiments. However, their supposedly more accurate CBS-QB3 calculations yielded $\Delta G_T=3.88$ kcal/mol and CBS-4M $\Delta G_T=3.39$ kcal/mol, which differs considerably from the experimental values for the gas-phase. According to another advanced computational technique, focal point analysis, the energy difference between tautomers converges to $\Delta E_T=3.98$ kcal/mol for the most accurate CCSD(T)/CBS//MP2/aug-cc-pVTZ model chemistry.[33] A very recent paper of Dabbagh et al. gives ΔG_T obtained for the gas-phase using B3LYP/6-311++G(d,p) basis set equal to 4.16 kcal/mol, and in water solution modelled by continuum PCM model $\Delta G_T=0.47$ kcal/mol.[34] Both these values are in close agreement with the experimental values.

As the presented literature has shown there are remarkable differences between the results of various theoretical approaches, especially regarding studies in solution. Moreover, it is often claimed in the literature that for proper estimation of solvation energy of molecules, which are able to create hydrogen bonds, it is necessary to take into account specific interactions between the solvent and the solute. However, the findings of Nagy et al. and of Dabbagh et al. show excellent agreement with experiments without including explicit water molecules and specific interactions. On the other hand, Monte Carlo simulations including many water molecules predicted wrong results. It is therefore of interest to check if specific solvent–solute interactions are important in this case, how many such interactions should be taken into account and