Azidoazomethine−Tetrazole Isomerism in Solution: A Thermochemical Study

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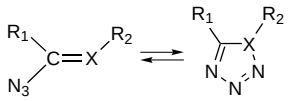
Introduction

The chemistry of the tetrazole ring is gaining increasing attention due to its importance in a variety of synthetic and industrial processes.[1] The balance between the deactivating effect of the three pyridine-type nitrogens and the influence of the single pyrrole-type nitrogen determines the reactivity of this heterocycle. Of particular interest is the azidoazomethine−tetrazole isomerism (Scheme 1), since this process is one of the main synthetic routes of tetrazole derivatives.[1] The equilibrium between azido and tetrazole species strongly depends on the nature of atom X, the substituent groups R_1 and R_2, the temperature, and the solvent.[2]

We have recently studied by using theoretical methods the sensitivity of the azidoazomethine−tetrazole isomerism of thiazole [3,2-*d*] tetrazole to both solvent and substituents.[3] Results showed the suitability of theoretical methods to predict the influence of these factors on the equilibrium. Here our purpose is to examine the effect of the temperature on the equilibrium by determining the enthalpy and entropy changes in solution in order to complete the thermochemical study of this reaction. Our interest is motivated by different reasons: (i) Even though theoretical results[3] indicated that cleavage of the tetrazole ring is exothermic in the gas phase, it is known experimentally that this process is endothermic in condensed phases.[4] (ii) Experimental values of the enthalpy (entropy) change for the azidoazomethine−tetrazole isomerism of thiazole [3,2-*d*] tetrazole are available, which allows a direct comparison.[5] This makes possible to test the suitability of computational methods to determine the relevant thermochemical data in solution, beyond the calculation of free energy changes.

Scheme 1



Methods

The solvent effect on thermochemical quantities was determined by using the *ab initio* HF/6-31G(d) version of the self-consistent reaction field (SCRF) MST continuum model,[6] also known as Polarizable Continuum Model.[7] Let us note that Monte Carlo−Free Energy Perturbation techniques, which are very useful to estimate the free energy of solvation, are less suitable for determining enthalpy and entropy changes, since the error in these quantities is sensibly larger than that for the free energy. In the MST method the free energy of solvation is determined by addition of electrostatic and nonelectrostatic (cavitation and van der Waals) components. The electrostatic term is computed by means of a set of imaginary charges spread over the solute/solvent interface, which are determined by solving the Laplace equation at the cavity surface (see ref 7c for details). The cavitation component is evaluated following Pierotti's scaled particle theory.[8] Finally, the van der Waals term is determined by using a linear relationship with the atomic contributions to the molecular surface area. Three different solvents were used in computations: water,[6a,b] chloroform,[6d] and carbon tetrachloride.[6c] The gas phase geometries optimized at the MP2/6-311G(d) level were used in calculations.

MST calculations were carried out with a modified version of MonsterGauss.[9] Calculations were carried out on SGI workstations in our laboratory.

Results and Discussion

In our previous study[3] the thermochemical data for the azidoazomethine−tetrazole isomerism of thiazole [3,2-*d*] tetrazole in the gas phase at 298 K were determined by using *state-of-the-art* quantum mechanical calculations.[10] The enthalpy change for cyclization of the azido group was estimated to be 1.6 kcal/mol, whereas the entropy

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(10) Gas phase energy differences were estimated by combining the results determined from quadratic single-and-double excitation configuration interaction with perturbative triple excitation and second-order Møller−Plesset (MP2) levels. These calculations were performed with Dunning's correlation-consistent valence triple-zeta basis augmented with both diffuse functions and functions of higher angular momentum and the 6-311++G(d,p) basis. Enthalpy and entropy differences were determined by adding the zero-point energy and thermal and entropic corrections to the energy differences determined at 298 K from the geometries optimized at the MP2/6-311G(d) level (see ref 3 for details).

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Table 1. Enthalpy (ΔH_{sol}; kcal/mol) and Entropy (ΔS_{sol}; cal K^{-1} mol^{-1}) Contributions to the Free Energy of Solvation (ΔG_{sol}; kcal/mol). Values Are Given Relative to the Enthalpy and Entropy of Solvation for the *cis*-Azido Isomer

	trans-azido			tetrazole		
solvent	ΔH_{sol}	ΔS_{sol}	ΔG_{sol}	ΔH_{sol}	ΔS_{sol}	ΔG_{sol}
carbon tetrachloride	−0.9	−2.6	−0.1	−2.0	−3.5	−1.0
chloroform	−1.1	−2.0	−0.5	−4.5	−7.4	−2.3
water	−3.0	−2.1	−2.4	−7.9	−3.7	−6.8

decreased by 6.4 cal K^{-1} mol^{-1} upon conversion of the azido form to the tetrazole species. Thus, opening of the tetrazole ring in the gas phase is an exoergic process, in which both enthalpy and entropy contributions are of similar magnitude. This finding is in contrast with the experimental evidence in condensed phases. Cleavage of the tetrazole ring is generally endothermic,[4,5] and accordingly higher temperatures should inhibit cyclization of the azido group. Moreover, the ring opening involves an entropy increase of approximately 10 cal K^{-1} mol^{-1}.[2a] Therefore, it is clear that the solvent effect must be explicitly accounted for in order to determine the thermodynamics of this process in solution.

In the context of SCRF methods the change in enthalpy arising upon transfer of the solute from the gas phase into solution can be estimated following the Gibbs−Helmholtz relation (eq 1), where ΔH_{sol} and ΔG_{sol} stand for the enthalpy and free energy of solvation.[7bc,11] Since ΔG_{sol} depends on the permittivity and on the cavity size, the temperature dependence of the free energy in eq 1 can be evaluated as indicated in eq 2,[12] where ϵ denotes the dielectric constant of the solvent at a given temperature and $\boldsymbol{n}$ is the vector normal to the cavity surface.[13]

$$\Delta H_{sol} = \Delta G_{sol} - T\left(\frac{\partial \Delta G_{sol}}{\partial T}\right)_P \qquad (1)$$

$$\frac{\partial \Delta G_{sol}}{\partial T} = \frac{\partial \Delta G_{sol}}{\partial \epsilon}\frac{\partial \epsilon}{\partial T} + \frac{\partial \Delta G_{sol}}{\partial \boldsymbol{n}}\frac{\partial \boldsymbol{n}}{\partial T} \qquad (2)$$

Table 1 gives the enthalpy and entropy of solvation of the tetrazole and *trans*-azido (the azido group *trans* to the pyridine-like nitrogen atom of the ring) species relative to the values of the *cis*-azido form. Results show the classical enthalpy/entropy compensation. Thus, the preferential solvation of *trans*-azido and particularly tetrazole is favored by the enthalpic term and disfavored by the entropic contribution. This can be understood from a microscopical point of view, since a better solute−solvent interaction energy should lead to a larger ordering of solvent molecules around the solute.

Table 2. Enthalpy (kcal/mol), Entropy (cal K^{-1} mol^{-1}), and Free Energy Differences in Solution. The values Are Given Relative to the Enthalpy and Entropy Change for the *Cis*-Azido Isomer

	trans-azido			tetrazole		
solvent	ΔH	ΔS	ΔG	ΔH	ΔS	ΔG
gas phase	2.5	0.7	2.3	1.6	−6.4	3.5
carbon tetrachloride	1.6	−1.9	2.2	−0.4	−9.9	2.5
chloroform	1.4	−1.3	1.8	−2.9	−13.8	1.2
water	−0.5	−1.4	−0.1	−6.3	−10.1	−3.3

The thermodynamic data in solution of the tetrazole and *trans*-azido species relative to the values of the *cis*-azido form are given in Table 2. The results reveal the large influence of solvation on the azidoazomethine−tetrazole isomerism. Thus, whereas the azido species is the most stable in the gas phase, the equilibrium is displaced toward the tetrazole species as the polarity of the solvent increases. This effect is mainly due to the contribution of the enthalpy of solvation, which reflects the preferential stabilization of the tetrazole isomer, i.e. the species with the largest dipole moment (6.3 Debyes versus 2.4 Debyes for the *cis*-azido form at the MP2/6-311G(d) level).[3] The results clearly reflect the change in the thermodynamic nature of the ring opening upon solvation. Thus, in contrast to the behavior in the gas phase, this process is clearly endothermic even in low polar solvents. However, if the enthalpic stabilization of the tetrazole isomer is not large enough as to compensate the loss in entropy arising upon ring cyclization, the isomerism will be displaced toward the azido forms, as it is experimentally[5] and theoretically[3] found for the equilibrium in carbon tetrachloride and chloroform.

Comparison of the present results with the available experimental data shows quantitative good agreement. With regard to the enthalpy change in the ring opening, the experimental data determined for thiazole [3,2-*d*] tetrazole in DMSO and nitrobenzene by Elguero et al. indicate values of 4.5 and 3.8 kcal/mol,[5d] which lie between our estimates for water (6.3) and carbon tetrachloride (0.4). Similar results were reported for the 4-methyl and 4,5-dimethyl derivatives.[5d] There are also data available for the cleavage of the tetrazole ring in related structures. Thus, the enthalpy change of benzothiazolotetrazole to 2-azidobenzothiazole has been estimated to be 4.7 in pyridine and 1.0 in dioxane.[4c] Indeed, the enthalpy change for the ring opening for 2-azidopyridimidine in DMSO amounts to 5.2 kcal/mol,[4d] whereas for 2-azido-4,6-dimethylpyrimidine was estimated to be 6.8 kcal/mol in chloroform.[4c]

With regard to the entropy change, it is generally assumed that the ring opening gives rise to a variation of 10 cal K^{-1} mol^{-1}.[2a] Particularly, the data for thiazole [3,2-*d*] tetrazole reported by Elguero et al. amount to 11.5 (DMSO) and 13.6 (nitrobenzene) cal K^{-1} mol^{-1}. Likewise, the change in entropy for 2-azidopyrimidine in DMSO was estimated to be 11.4 cal K^{-1} mol^{-1},[4d] whereas for 2-azido-4,6-dimethylpyrimidine in chloroform was 19.5 cal K^{-1} mol^{-1}.[4c] Again these values are close to our estimates, which lie in the range 10−14 cal K^{-1} mol^{-1} for the solvents considered in the study.

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(12) It must be noted that the partial derivatives of ΔG_{sol} in eq 2 were approximated considering only the electrostatic component of the free energy of solvation, since this term is expected to dominate the differences between azido and tetrazole species. This point was confirmed by a series of test calculations, which indicated that the contributions of nonelectrostatic terms to the temperature dependence of ΔG_{sol} roughly canceled between the different isomers.

(13) The values of $(\partial \Delta G_{sol}/\partial \epsilon)$ and $(\partial \Delta G_{sol}/\partial \boldsymbol{n})$ were estimated numerically from the ΔG_{sol} values calculated at $\epsilon \pm 0.1$ and $\lambda \pm 0.01$, λ being the factor that scales the cavity size in the MST continuum model (see ref 6 for details). No significant differences in the values of derivatives were found when other increments were used. The values of the temperature dependence of the permitivity $(\partial \epsilon/\partial T)$ and the thermal expansion coefficient $(\partial \boldsymbol{n}/\partial T)$ were taken directly from the literature or determined from the corresponding data: (a) *Handbook of Chemistry and Physics*, 68th ed.; West, R. C., Ed.; CRC Press: Boca Raton, 1987/88. (b) Timmermans, J. *Physico-Chemical Constants of Pure Organic Compounds*; Elsevier: New York, 1950.

The encouraging agreement between experimental and theoretical results supports the suitability of theoretical methods to determine the thermochemical data for reactions in condensed phases beyond the information provided by free energy changes. Knowledge of this information is essential to characterize the equilibrium of chemical reactions, which in turn is necessary to design the most favorable synthetic conditions. Present results show that computational techniques can be used as an alternative to the experimental determination, which sometimes can be limited by technical constraints. Finally, an accurate comparison of experimental and calculated trends of free energy and enthalpy of solvation will be useful for further refinements in the current theoretical models.

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