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Effect of the 5-Substituent on the Tetrazole–Azide Isomerization in Tetrazolo[1,5-a]pyridines by Ab Initio Calculations

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Abstract—The effect of substituents CH_3, OH, Cl, OCH_3, NO_2 and COOH at the 5-position in tetrazolo[1,5-a]pyridines, on the tetrazole–azide equilibrium, was investigated at the 6-31G**/MP2 level of theory. For both, the parent and 5-CH_3 compounds, the tetrazole forms are largely favored, while the other substituents-OH, Cl, OCH_3, and NO_2-stabilize the azide isomer. With the COOH group, the tetrazole and azide forms are predicted to be in equilibrium in nearly equal amounts. The influence of these groups on the transition state (TS) was also studied. In general it is observed that, groups which stabilize the azide isomer, lower the E_{act} of the isomerization reaction, and conversely, those that favor the tetrazole form, raise the E_{act} of this reaction, relative to the unsubstituted compound. The TS has a close resemblance to the tetrazole structure. © 2000 Published by Elsevier Science Ltd.

Introduction

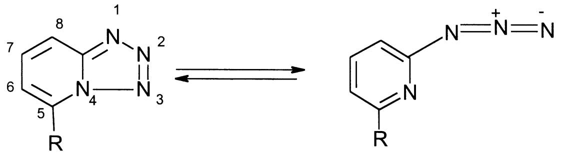
Heterocyclic azides are known to spontaneously cyclize to give the fused tetrazole form or more generally exist as an equilibrium mixture. This has been described variously in the literature as a tautomerism, as an azidomethine-tetrazole (imideamide-tetrazole) equilibrium, as a 1,5-dipolar cyclization and as a valence isomerization.[1,2] A variety of heterocyclic groups like tetrazolopyridines, tetrazolopyridazines, tetrazolopyrimidines, tetrazoloazines, tetrazolopurines etc. have been reported to exhibit the tetrazole–azide isomerization.[3] The two forms i.e. the tetrazole and azide, have contrasting chemical properties. The tetrazole ring is electronegative while the azido is electropositive. The tetrazole–azide isomerization is governed by the electron donating capacity of the heterocycle to which the tetrazole ring is fused. Thus, electron withdrawing groups favor the azide and vice versa electron donating groups stabilize the tetrazole structure. Besides the influence of the substituent on the tetrazole–azide equilibrium, the nature of the solvent (protic or aprotic) and its polarity also play a dominant role on the extent of equilibrium. Furthermore, a high temperature is seen to favor the azide state.

There are quite a few reports[4–6] (all experimental works) on the tetrazole–azide equilibrium in tetrazolo[1,5-a]pyridines (Fig. 1). Most studies have looked at the effect of substitution at the 6 and/or 8 positions on the tetrazole–azide equilibrium. Groups at the 6 and 8 positions do not show the same effect on the equilibrium. Thus, while 8-NO_2, 8-COOH and 8-Cl favor the tetrazole forms, these same moieties at the 6-position establish an equilibrium between the tetrazole and azide isomers. There is just one example[6] of a 5-Cl group on this equilibrium. We were interested in systematically examining the effect of substitution at the 5-position on the tetrazole–azide equilibrium. The 5-position being nearest to the 'reaction center' (the dissociating N3–N4 bond) could be expected to dramatically modulate the equilibrium reaction via an electronic and steric effect.

We have examined the influence of various substituents (R=CH_3, OH, Cl, OCH_3, NO_2 and COOH) at the 5-position in tetrazolo[1,5-a]pyridines (Fig. 1) on the stabilities of the tetrazole and azide isomers by ab initio calculations. In addition, the effect of these groups on the transition state (TS) has also been studied.

Methodology

Ab initio calculations were carried out with the Turbomole program[7] (v 2.3, MSI, USA) running on a SGI Iris Indigo



Tetrazolo[1,5-a]pyridine **Azidopyridine**

R = H, CH_3, OH, Cl, OCH_3, NO_2,

Figure 1. Tetrazolo[1,5-a]pyridines and their corresponding azide isomers.

Keywords: tetrazolo[1,5-a]pyridine; tetrazole–azide isomerization; TS; ab initio calculations.

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computer. Geometry optimization was done at the 6-31G** level of theory. Electron correlation energy using second-order Möller–Plesset perturbation theory with the 'frozen core' option was then calculated for the optimized geometry. All optimizations were run without conformational or symmetry constraints. Ground states were optimized by the EF algorithm to a gradient of 0.00001 or lower.

Transition states were determined by varying the N3–N4 distance and optimizing the remaining structural parameters for each choice of the N3–N4 distance. This is referred to in the literature as the 'distinguished-coordinate' approach.[8] At the saddle point on this graph, the calculate transition states option was switched on, in which case the EF algorithm optimizes the TS by maximizing along the lowest Hessian mode.

All ground and transition states were rigorously characterized by computing vibrational frequencies. Ground states were confirmed by the absence of any imaginary (negative) frequency, while transition states were identified by the presence of one and only one imaginary frequency.

Results and Discussion

The energies of the parent and substituted tetrazoles and azides at the 6-31G**/MP2 level of theory are given in Table 1. The difference in energies of the two ground states are also listed in this table. In the azides, the N1–N2–N3 angle is on average 173°, showing that the azido group is linear and not bent, this is in agreement with an early reported MO calculation.[9]

For the unsubstituted compound (R=H) and the molecule with a 5-CH_3 group, the tetrazole is predicted to be more stable. The other functional groups — Cl, OH, OCH_3 and NO_2 — favor the azide isomer. Of all the groups studied by us, the NO_2 has the largest effect on the equilibrium. It is seen to stabilize the azide by as much as 7.0 kcal/mol over the tetrazole. The tetrazole and azide forms are predicted to be in equilibrium for the 5-COOH group.

The effect of the methyl group corresponds to Messmer and Hajós's statement that the 'electron releasing methyl group enhances the stability of the tetrazole form'.[10]

The behavior of 5-NO_2 contrasts with the 8-NO_2, where only the tetrazole form has been observed at 298 K, but falls in line with the tenet that electron withdrawing groups favor the azide isomer.[3]

The 5-COOH group matches the effect of the 6-COOH (but not the 8-COOH) in that both these positions (i.e. 5 and 6) promote an equilibrium of the tetrazole and azide forms.[4]

Table 1. 6-31G**/MP2 energies (kcal/mol) of tetrazoles and azides

R	Tetrazole (T)	Azide (A)	$E_T - E_A$
H	−257 705.1	−257 701.2	−3.9
CH_3	−282 298.0	−282 292.2	−5.8
OH	−304 785.7	−304 787.5	1.8
Cl	−545 734.0	−545 735.5	1.5
OCH_3	−329 361.4	−329 363.8	2.4
NO_2	−385 696.6	−385 703.6	7.0
COOH	−375 773.0	−375 772.7	−0.3

To the best of our knowledge, the influence of OH and OCH_3 groups on the equilibrium has never been investigated in this system. The effect of the 5-OH and 5-OCH_3 groups goes against the general remark that electron releasing groups favor the tetrazole form.[3] This means that for these groups at the 5-position in this reaction, their inductive effect dominates the resonance effect.

The outcome of the 5-Cl substituent is along expected lines for an electron withdrawing group but is opposite to that observed for the 8-Cl.[4]

In order to compare the computed ab initio energies with the experimentally measured heat of isomerization, it is necessary to make corrections for the zero point energy (ZPE), thermal corrections at 298 K and the work done (PΔV) in this reaction. For isomerization this last value is zero. We have computed these corrections and calculated the enthalpy of isomerization of the tetrazole–azide equilibrium for the 5-Cl substituent, to be 3.8 kcal/mol. This value compares excellently with the experimental figure of 3.4 ± 0.5 kcal/mol.[6] This indicates that 6-31G**/MP2 energy is a reliable prediction of the stabilities of the tetrazole and azide forms of these molecules.

Transition states (TS)

The TS have a geometry that closely resemble the tetrazole structure and are thus to be inferred as early TS. The N3–N4 distance in the TS for this set of molecules varies from 1.9 to 2.02 Å and the N1–N2–N3 angle ranges from 128.9 to 133.9° (showing it to be heavily bent). These values in the TS and corresponding bond lengths and angles in the ground states for comparison are given in Table 2.

The ab initio energies of the TS are tabulated along with the activation energies (E_{act}) relative to the tetrazole form in Table 2.

The E_{act} for the 5-CH_3 compound is ca. 1 kcal/mol higher that the unsubstituted molecule. The methyl group is the only functionality among those investigated that raises the E_{act} above the unsubstituted analog. The most profound effect on the TS is shown by the NO_2 group, it lowers the E_{act} by nearly 8.6 kcal/mol relative to the unsubstituted compound. The other moieties (OH, Cl, OCH_3, NO_2 and COOH) are all seen to lower the E_{act} relative to the unsubstituted compound, by amounts ranging from 3.6 to 5.4 kcal/mol.

Conclusions

Ab initio 6-31G**/MP2 energies can reliably be used to predict the effect of substitution on the tetrazole–azide equilibrium. This can be gauged from the calculated enthalpy of isomerization for the 5-Cl compound, which is in excellent agreement with the experimentally reported value.

A methyl group at the 5-position is seen to favor the

Table 2. Energies (kcal/mol) and geometries of TS

R	TS	E_{act} $E_{TS}-E_T$	Geometry of TS		
			N3–N4 dist (A)[a]	N1–N2–N3 angle (°)[b]	N2–N3–N4 angle (°)[c]
H	−257 679.0	26.1	2.01(1.40)	133.2(173.1)	90.0(104.9)
CH_3	−282 271.0	27.0	2.02(1.40)	133.9(173.2)	89.4(105.0)
OH	−304 763.7	22.0	1.97(1.41)	132.0(172.9)	90.9(104.6)
Cl	−545 711.6	22.4	1.94(1.32)	130.9(172.8)	91.8(105.7)
OCH_3	−329 340.7	20.7	1.99(1.40)	132.5(173.0)	90.5(105.0)
NO_2	−385 679.1	17.5	1.90(1.41)	128.9(172.7)	93.3(104.8)
COOH	−375 750.5	22.5	1.97(1.40)	131.5(173.0)	91.2(105.0)

[a] In parenthesis is the N3–N4 bond length in the tetrazole.
[b] The N1–N2–N3 bond angle in the azide is entered in parenthesis.
[c] The corresponding N2–N3–N4 bond angle in the tetrazole is shown in brackets.

tetrazole form, while any group having an electronegative atom directly attached to the 5-position, stabilizes the azide isomer. As regards their effect on the TS, it is seen that, those functional groups that stabilize the azide, decrease the activation energy of the TS for isomerization and vice versa, the moieties that favor the tetrazole form raise the E_{act} of this reaction, relative to the unsubstituted compound (R=H). The COOH is the only exception to the above quoted rule.

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