A Theoretical Study on Intramolecular Cyclization of Azidobenzotriazine to Tetrazolobenzotriazines

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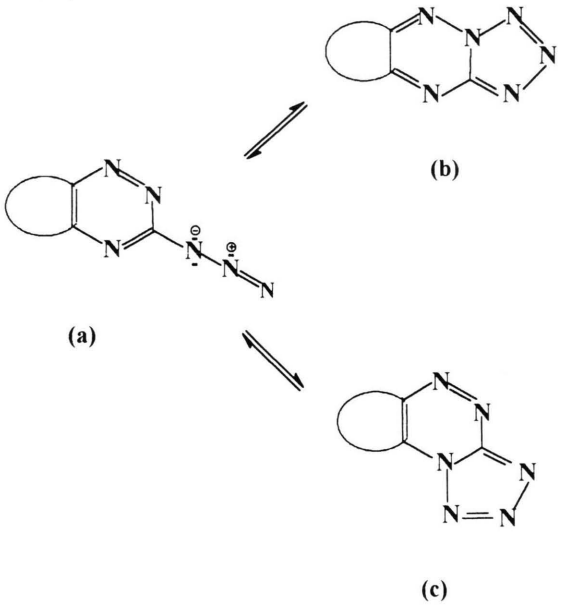
Z. Naturforsch. **51a**, 1012–1018 (1996); received March 18, 1996

The cyclization equilibrium of 3-azidobenzo[1,2,4]triazine (**1a**) with tetrazolo[5,1-b]benzo[1,2,4] triazine (linear isomer, **1b**) and tetrazolo[5,1-c]benzo[1,2,4]triazine (angular isomer, **1c**) is investigated computationally using the molecular orbital MNDO-SCF method. The results suggest that the higher reactivity of atom N(4) with respect to N(2) towards the cyclization is due to: (i) The negative charge density upon N(4) is 1.3 time larger than that upon N(2); (ii) In the highest occupied molecular orbital (HOMO) the coefficient at N(4) is 2.4 times larger than that at N(2); (iii) The heat of reaction to (**1c**) and (**1b**) are calculated to be -74.9 and -14.8 kJ mol^{-1}, respectively; (iv) The thermodynamic stabilization of the angular isomer (**1c**) is 60.1 kJ mol^{-1} larger than that of the linear isomer (**1b**), and (v) The potential barrier heights calculated for the cyclization favour the angular product. From these considerations and the perturbation theory, the calculated yield of the cyclization reaction is $70.8 \pm 0.1\%$ of **1c**, which is in good agreement with the experimental yield 64%.

Introduction

Generally, the 3-azido[1,2,4]triazine system (**a**) cyclizes in equilibrium processes either with the nitrogen atom N(2) to form the linear tetrazolo derivative [5,1-b][1,2,4] system (**b**), or with the nitrogen atom N(4) leading to the angular tetrazolo derivative [5,1-c][1,2,4] system (**c**) (see Fig. 1 for numbering of the atoms).



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Several examples regarding this dual possibility of cyclization are discussed in the literature [1–8]. In these studies, the effect of substituents, as well as the type of ring attached to the carbon atoms C(5) and C(6) of the triazine ring have been investigated. This dual possibility of cyclization involving the atoms N(2) or N(4) is also encountered in the corresponding 3-hydrazine derivatives [9–11].

Contradictory observations have been reported regarding the structure of the product of cyclization to be either compound **b** or **c** [1, 4]. Attempts to rationalize the formation of one isomer in preference to the other are scarce in the literature. The application of Clar's rule was usually used to interpret the relative stability of polyfused carbocycle isomers [5, 12]. The isomer with greater numbers of Clar's circles is supposed to be the more stable isomer, having the higher degree of aromatic stability [5].

The main goal of the present work is to study the effect of molecular structure on the regioselectivity of this type oc cyclization. The cyclization equilibrium of 3-azidobenzo[1,2,4]triazine (**1a**), tetrazolo[5,1-b]benzo-[1,2,4]tetrazine (**1b**) and tetrazolo[5,1-c]benzo[1,2,4]-tetrazine (**1c**) is selected as a model for this study. Molecular orbital methods have produced valuable contributions to the understanding of the nature of structure-activity relations. Among the most important are the charge densities on the reactive centers, frontier molecular orbital energies and coefficients, heats of reaction and stabilization energy differences

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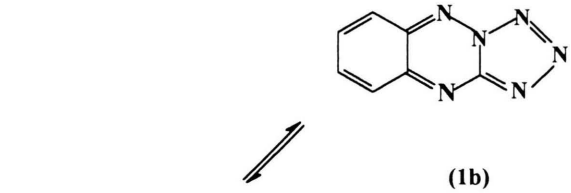
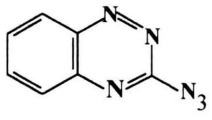
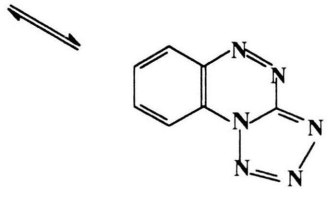
between the products. Since *ab initio* methods are relatively expensive in such calculations, semiempirical calculations have been usually used. One of the most successful semiempirical methods for the calculation of molecular properties is the MNDO molecular orbital method [13]. This method is used to study both the optimized conformations and the electronic structures of different azido-tetrazolo equilibrium isomers as well as the transition states leading to the cyclic isomers. We hoped to understand not only why one of the tetrazole isomers is preferentially formed, but also to get a general mechanism for this type of cyclization.



(1b)



(1a)



(1c)

Computational Aspects

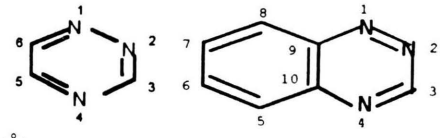
All calculations were performed using the semiempirical all-valence-electrons molecular orbital MNDO-SCF method [13, 14]. As implemented in the molecular orbital package MOPAC [15] version 5.0. The equilibrium geometries for azido and tetrazolo compounds were generated in three steps: firstly, we have built the triazine ring by taking the starting geometry form x-ray crystallographic data of the triazine derivative [1], secondly, with standard values for bond lengths and bond angles as starting point we calculated benzotriazine, finally we have built the azido and tetrazolo structures in similar way. The geometries of all compounds were found by minimizing the energy with respect to all geometrical parameters, namely, bond lengths, bond angles and dihedral angles. The transition state structures (**TS-1b**) and (**TS-1c**), shown in Fig. 5, were determined by minimizing the energy with respect to different increments in the reaction coordinate, bond distance N(2)–N(7) in **TS-1b**, N(4)–N(7) in **TS-1c** and accordingly bond angles C(3)N(5)N(6) and N(5)N(6)N(7).

Results and Discussion

Geometries and Electronic Structures

The optimized geometries of 1,2,4-triazine and 1,2,4-benzotriazine are represented in Table 1. The results show that the two structures are planar, and the bond lengths N(1)–N(2) and C(3)–N(4) in benzotriazine are significantly shorter than those for triazine itself while the other C–N bond lengths are longer than the corresponding distances for triazine. These data indicate that the double bond character of the N(1)–N(2) and C(3)–N(4) bonds is more pronounced in benzotriazine than in the corresponding

Table 1. The optimized geometries for 1,2,4-triazine, 1,2,4-benzotriazine and the x-ray crystallographic values for 5-(4-chlorophenyl) derivative from [1] (in brackets).



Bond lengths (Å)			
N(1)–N(2)	1.274 (1.335)		1.247
N(2)–C(3)	1.373 (1.314)		1.401
C(3)–N(4)	1.375 (1.339)		1.326
N(4)–C(5)	1.349 (1.317)	N(4)–C(10)	1.382
C(5)–C(6)	1.414 (1.401)	C(9)–C(10)	1.432
C(6)–N(1)	1.365 (1.317)	C(9)–N(1)	1.401
		C(5)–C(10)	1.439
		C(5)–C(6)	1.384
		C(6)–C(7)	1.432
		C(7)–C(8)	1.384
		C(8)–C(9)	1.434
Bond angles (degree)			
N(1)–N(2)–C(3)	120.7 (117.1)		121.2
N(2)–C(3)–N(4)	123.2 (127.2)		123.8
C(3)–N(4)–C(5)	116.3 (115.9)	N(1)–C(5)–C(8)	121.0
N(4)–C(5)–C(6)	120.1 (118.4)	C(5)–C(10)–C(9)	119.4
C(5)–C(6)–N(1)	121.5 (122.5)	C(10)–C(9)–N(1)	118.8
C(6)–N(1)–N(2)	118.2 (118.8)	C(9)–N(1)–N(2)	120.2
		C(6)–C(5)–C(10)	119.2
		C(5)–C(6)–C(7)	121.2

triazine. These bond lengths, as well as the π-bond order values (*vide infra*) show that the six π-electrons in the benzene ring of benzotriazine are preserved.

The charge densities and π-bond orders for triazine and benzotriazine are shown in Figure 1. The negative charge density is located mainly upon N(4) and N(2). Moreover, the charge upon N(4) is 1.7 times than that upon N(2) in both compounds. The π-bond order values for triazine would with a Kekule's structure having a single bond between N(1) and N(2) while those for benzotriazine would be more in line with a double bond at the corresponding site. This would conserve the aromaticity of the benzene ring in the latter case.

A schematic drawing of the π-MOs of 1,2,4-triazine and benzotriazine is given in Figure 2. The MNDO-calculated and the experimental PE-spectra [16] of π_1 and π_2 of triazine are in good agreement (average deviation 0.25 eV). On introducing the benzene ring to triazine, the E_{HOMO} is raised and the E_{LUMO} is lowered as might be expected by increasing the conjugation of the π-system.

The optimized geometrical parameters for 3-azido[1,2,4]benzotriazine (**1a**), tetrazolo[5,1-b]benzo-[1,2,4]tetrazine (**1b**) and tetrazolo[5,1-c]benzo[1,2,4]-

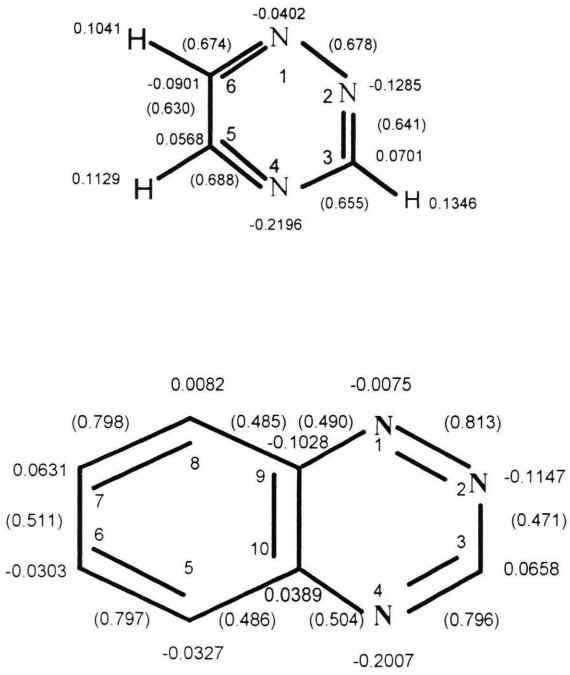


Fig. 1. Calculated charge densities and π-bond orders (in brackets) for 1,2,4-triazine and 1,2,4-benzotriazine.

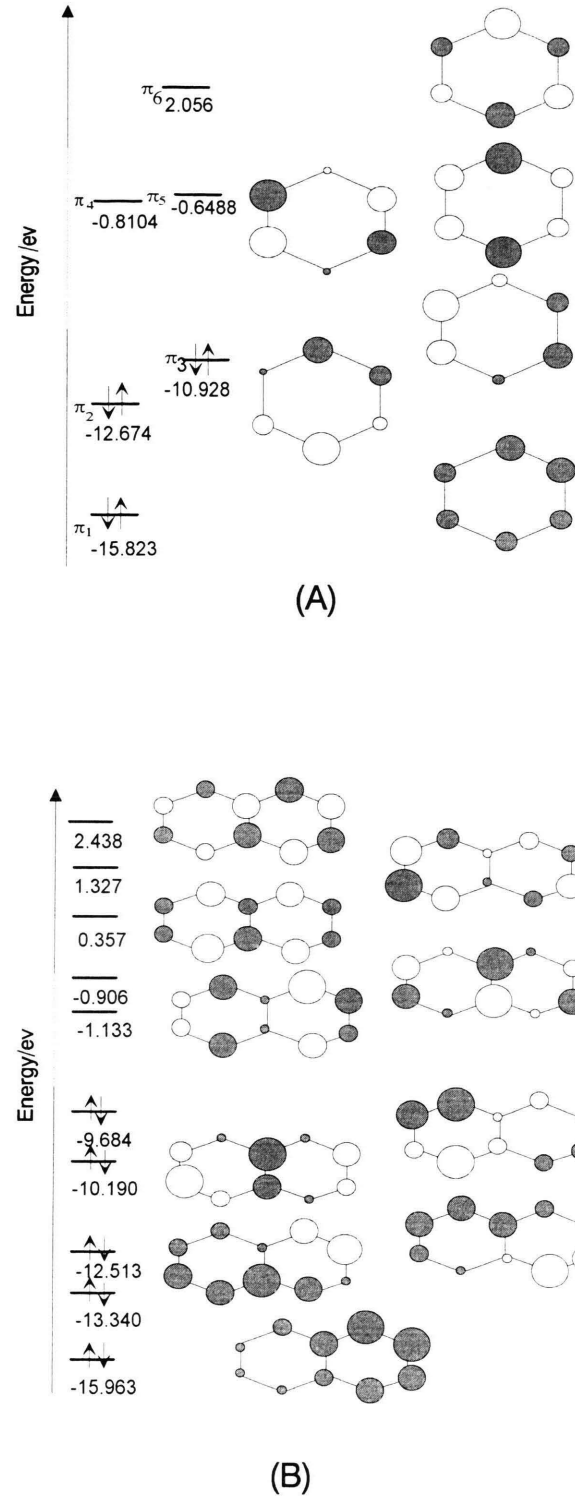


Fig. 2. Schematic drawing of the different π-MO's of 1,2,4-triazine and benzotriazine.

Table 2. The optimized geometries* of 3-azido[1,2,4]benzotriazine (**1a**), tetrazolo[5,1-b]benzo[1,2,4]tetrazine (**1b**) and tetrazolo[5,1-c]benzo[1,2,4]tetrazine (**1c**).

	(**1a**)	(**1b**)	(**1c**)
Bond lengths (Å)			
N(1)–N(2)	1.246	1.319	1.231
N(2)–C(3)	1.412	1.436	1.413
C(3)–N(4)	1.338	1.368	1.418
C(3)–N(5)	1.405	1.359	1.351
N(5)–N(6)	1.272	1.321	1.325
N(6)–N(7)	1.123	1.279	1.377
N(1)–C(12)	1.395	1.344	1.421
N(4)–C(13)	1.378	1.334	1.411
N(7)–C(2)	–	1.350	–
N(7)–C(4)	–	–	1.344
Bond angles (degree)			
N(1)–N(2)–N(3)	120.3	119.8	119.9
N(2)–C(3)–N(4)	124.6	120.2	120.3
C(2)–N(4)–C(13)	115.5	120.8	120.8
N(5)–C(3)–N(2)	119.4	110.5	110.2
N(6)–N(5)–C(3)	117.7	106.5	106.7
N(7)–N(6)–N(5)	164.9	114.8	113.9

* See Fig. 2 for numbering of the atoms.

tetrazine (**1c**) are shown in Table 2. Inspection of the data indicates that all structures are planar and the azido group in **1a** has a nonlinear geometrical structure, which is consistent with the experimental work on similar structures [17]. The bond lengths N(1)–N(2) in **1a** and **1c** are nearly equal (1.24 ± 0.01) and shorter than that for **1b**. On the other hand, the bond lengths N(1)–C(12) and N(4)–C(13) are shorter in **1b** than those in **1a** and **1c**. These considerations, together with the values of π-bond order, favour the drawing of the localized structures for these compounds as represented in Scheme 2.

The charge densities and π-bond orders for **1a**, **1b** and **1c** are represented in Figure 3. The π-bond order values for the bonds N(1)–N(2) in **1a** and **1c**, N(1)–C(12) and N(4)–C(13) in **1b**, show a double bond character ($P_{ij} = 0.8 \pm 0.02$) which confirms the localized structures for these compounds, as we mentioned before.

The geometries and energies of the frontier molecular orbitals (HOMO's and LUMO's) of the different components are represented in Figure 4.

Reactivity and Mode of Cyclization

The 1,2,4-triazine derivatives with the dual possibility of cyclization could be regarded as ambident reagents. The regioselectivity may be governed by different factors, namely the relative charge densities and the atomic orbital coefficients of the HOMO at the competitive reaction centers, the relative potential energy barrier and the relative thermodynamic stabilization of the products.

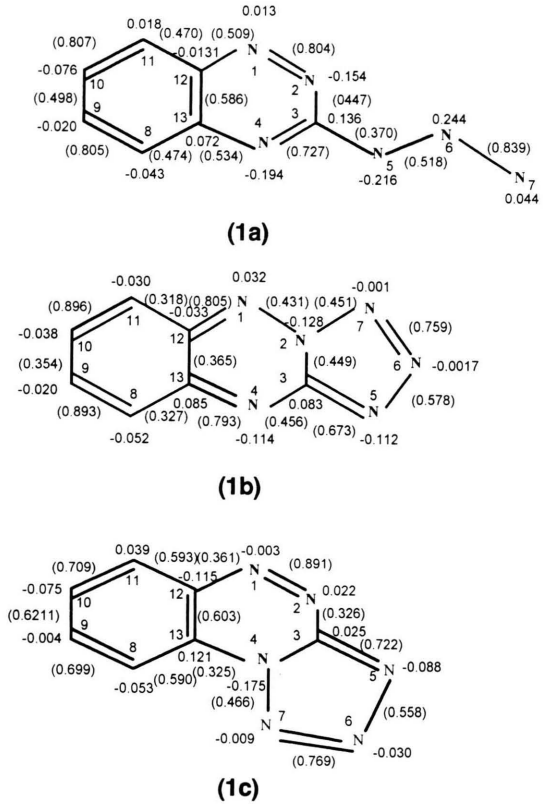


Fig. 3. Calculated charge densities and π-bond orders for **1a**, **1b** and **1c**.

This problem could be approached within the framework of Generalized Perturbation Theory [18, 19], where in the studied case the electron donor and electron acceptor sites are linked by a common molecular orbital, HOMO, self-perturbation [20]. The perturbation equation for such a case can be reduced to be represented by the equation [20]

$$\Delta E = q_i q_j / R_{ij} \varepsilon + 2 C_i C_j \beta_{ij} ,$$

where ΔE is the energy change due to the partial bond formation between an electron acceptor atom i (N(7)) and an electron donor atom j (N(2) or N(4)) in a solvent of effective dielectric constant ε, q_i is the electronic charge on the terminal nitrogen N(7) of the azido group, q_j the electronic charge on either N(2) or

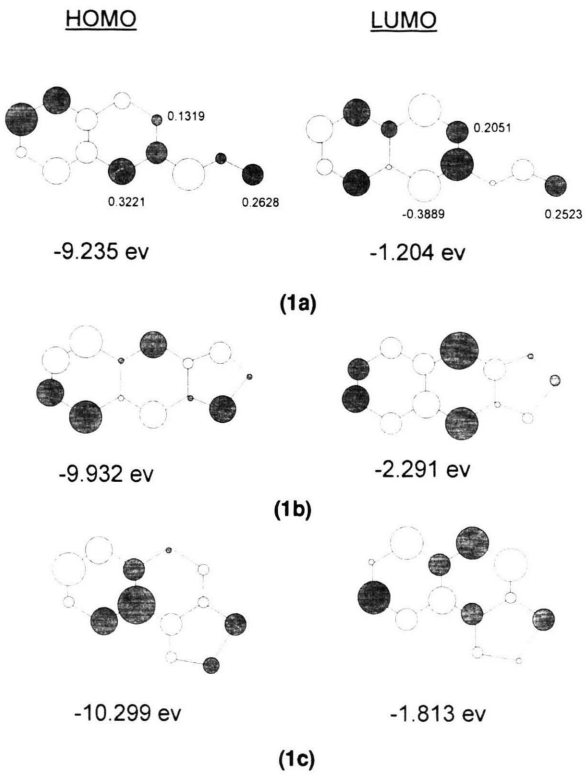


Fig. 4. Frontier molecular orbitals of **1a**, **1b** and **1c**.

N(4) of the triazine ring, C_i the atomic orbital coefficient at N(7) in the HOMO, C_j the atomic orbital coefficient at N(2) or N(4) in the HOMO, R_{ij} the distance between the two centers i and j, and β_{ij} the change in the resonance integral between the interacting orbitals at atoms i and j at the distance R_{ij}.

According to this equation, ΔE depends basically on two terms: an electrostatic term (first term) which has a minor influence, and a covalent term (second term) which has the lead in determining ΔE. Consideration of the second term alone would favour the cyclization of the angular isomer (**1a** → **1c**) over that of the linear isomer (**1a** → **1b**) by a factor of 2.44, where the ratio of the stabilization term (for the cyclization **1a** → **1c**/**1a** → **1c**) is $0.1693\,\beta_{ij}/0.0693\,\beta_{ij}$. Accordingly, the isomer **1c** is supposed to be 70.9% of the products. On the other hand, the first term, which plays the minor role in this process, favours also the cyclization **1a** → **1c** over **1a** → **1b** by a factor of 1.25 times products, i.e., the **1c** isomer is supposed to be 55.5% of the products. Therefore, **1c** is expected to be the main product of this cyclization process with an average value of 70.9 ± 0.1 (for $R_{ij} = 2$ Å, $\varepsilon = (1 \rightarrow 80)$ and $\beta_{ij} = 4.6$ eV). This value is in agreement with the observed behavior both in solution and solid state, where the product **1c** was found to constitute 64%.

In the transition states, **TS-1b** and **TS-1c**, the forming bonds N(2)–N(7) and N(4)–N(7) are long (ca. 2.0 Å), and there is an increase in the charge on atom N(7), atom N(2) in **TS-1b**, and atom N(4) in **TS-1c** (see Figure 5). The N(1)–N(2) and C(3)–N(4) bonds in **TS-1b** loose a considerable amount of double bond character (smaller bond orders), while the N(1)–C(12) and N(4)–C(13) bonds gain a double bond character (larger bond orders).

The calculated heats of formation for the different components and transition states are given in Table 3.

Table 3. Calculated heats of formation.

	1a	**TS-1b**	**1b**	**TS-1c**	**1c**
ΔH_f (kJ mol^{-1})	560.8	858.0	545.9	822.0	485.8

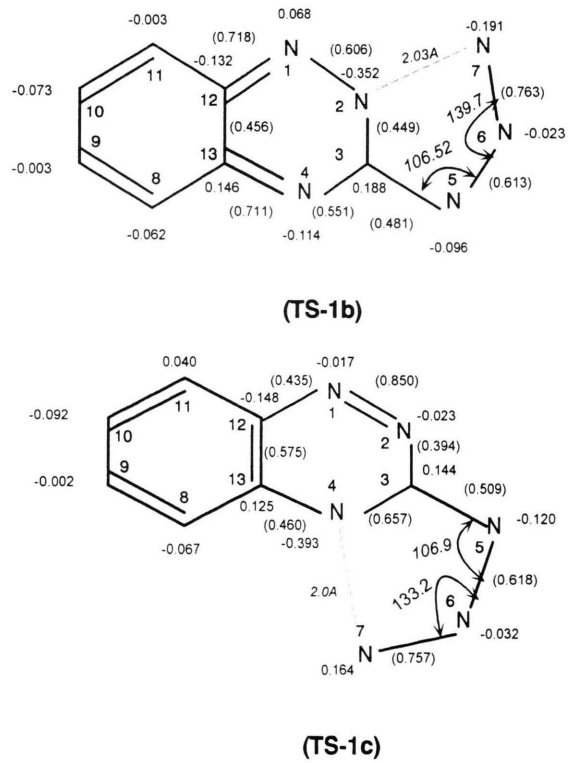


Fig. 5. Calculated charge densities, π-bond orders and optimized geometries of **1b-TS** and **1c-TS**.

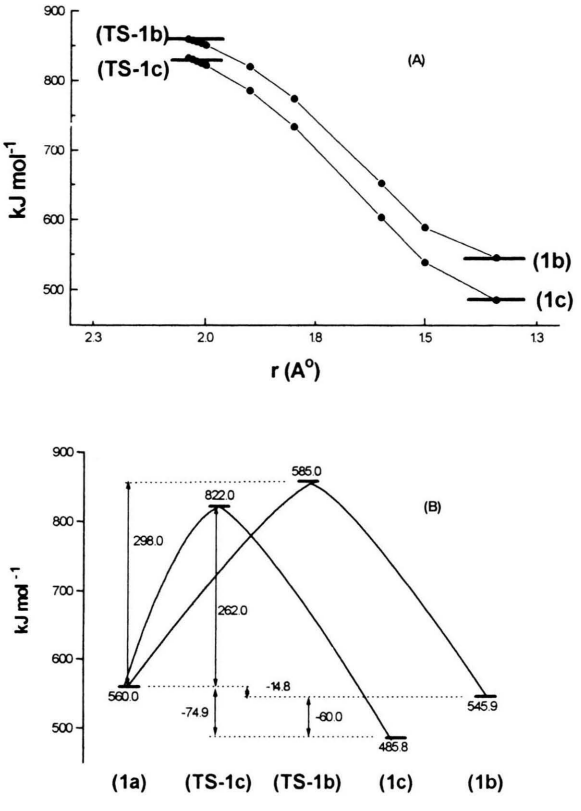


Fig. 6. (A) Energy profiles of **1b** → **TS-1b** and **1c** → **TS-1c** where r(Å) is the distance N(2)–N(7) in the first and N(4)–N(7) in the second process; (B) energetic scheme for the cyclization of **1a** to **1b** and **1c** via **TS-1b** and **TS-1c** respectively.

The heat of formation for the cyclization **1a** → **1b** and **1a** → **1c** are −14.8 and −74.9 kJ mol^{-1}, respectively. The corresonding potential energy barriers heights are calculated to be 297.2 and 261.2 kJ mol^{-1}, However, these values are large and do not seem to be in agreement with the corresponding experimental data; they still reflect the comparative reactivities of the both steps.

It is worth mentioning that the calculated thermodynamic stabilization of the angular isomer (**1c**) with respect to the linear isomer (**1b**) is 60.1 kJ mol^{-1} larger (see Figure 6). This extra-stabilization seems to suggest a larger aromatic character of **1c** with respect to **1b**.

In Conclusion, this study demonstrates the reliability of the MNDO-method as a powerful computational tool not only in the study of isolated molecular systems, but also in the elucidation of organic reaction mechanism as well. We have utilized this method to elucidate the reaction mechanism of cyclization of azidobenzotriazine to tetrazolobenzotriazine and correctly predicted the major isomeric product. It has been shown theoretically that the reaction pathway is governed mainly by the geometry of the HOMO and charge densities of the reactive centers. Undoubtedly, introduction of a group causing steric hindrance or electron withdrawing group could alter the direction of cyclization.

Acknowledgement

We thank Prof. Dr. J. Fleischhauer, RWTH-Aachen, for valuable discussions during the preparation of this paper.

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