



Semiempirical and ab initio transition state calculations for the transformation of N-acetyltetrazoles into corresponding 1,3,4-oxadiazoles

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Abstract

The transformation of 2-acetyl-5-substituted-tetrazoles into the corresponding 1,3,4-oxadiazoles was studied with the MOPAC semiempirical and GAUSSIAN ab initio methods. Two mechanisms, one with two transition states and the other with three, were elucidated by MOPAC. The first mechanism supported by PM3 and MNDO has a two-step, almost concerted, mechanism for the elimination of a nitrogen molecule from the tetrazole ring and formation of the oxadiazole product from an open-chain intermediate through carbon C₅ and acetyl oxygen bond formation. The second mechanism supported by AM1 and MINDO/3 breaks the elimination of the nitrogen molecule into two steps: first breaking the N₄–C₅ and then the N₂–N₃ bonds. Even when the AM1 and MINDO/3 transition state structures were optimized by PM3 and MNDO, the obtained transition states present only one bond breaking. The HF/STO-3G and HF/3-21G ab initio methods agree with the first mechanism where two bonds are breaking almost simultaneously. Despite the disagreement in the mechanism of the nitrogen elimination, the transition state that presents the product formation from open-chain intermediates is quite similar for all methods studied. The semiempirical calculation of this transition state is possible only if it is assumed that it has biradical character. The activation energies calculated by PM3 seem to be insensitive to the nature of the substituents.

1. Introduction

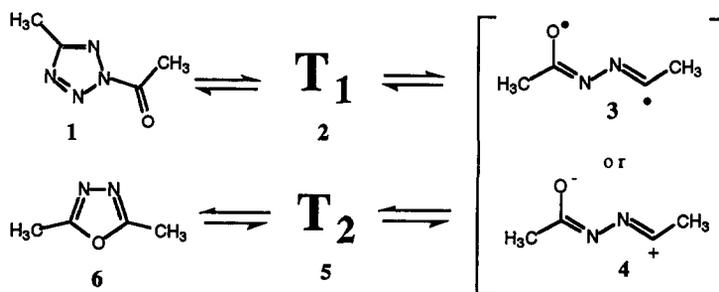
Recently, we reported a very efficient method for the preparation of a wide variety of acidic acid derivatives via N-acyltetrazole intermediates [1]. Other results [2], as well as our own, suggest extreme temperature sensitivity of the N-acetyltetrazole intermediate and thus the formation of a considerable amount of a corresponding oxadiazole

by-product. That problem can be easily overcome if the nucleophilic displacement reaction is performed at –15°C or even lower temperatures [1]. The reactivity of N-acyltetrazole derivatives is remarkably high in comparison to other azole derivatives. We have determined this fact experimentally as well as by semiempirical and ab initio calculations [3].

Oxadiazoles are very important compounds having a wide variety of biological activities, and consequently we decided to examine closely the transformation of organic acids and tetrazoles to these valuable substances in a one-pot synthesis

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Scheme 1.

[4]. We have succeeded in accomplishing this task and the results will be reported elsewhere [18].

To our great surprise we were not able to find any experimental or theoretical studies of the transformation of N-acyltetrazoles into the corresponding oxadiazoles. In this paper, we would like to report our study of this transformation using as a model the conversion of 2-acetyl-5-methyltetrazole into 2,5-dimethyl-1,3,4-oxadiazole by AM1, PM3, MINDO/3 and MNDO MOPAC semiempirical and STO-3G, 3-21G and 6-31G GAUSSIAN 92 ab initio calculations.

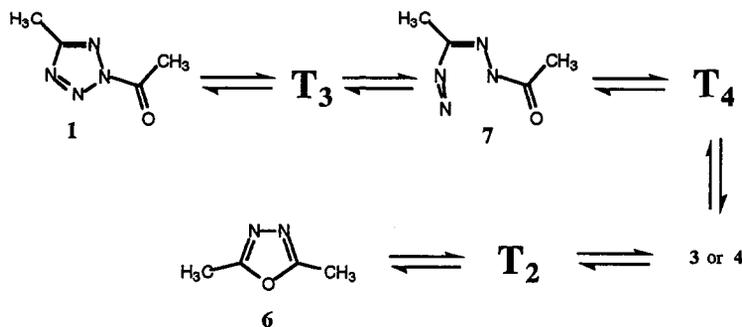
2. Procedures and methods

All calculations were performed on an IBM compatible 486 DX2 66MHz computer with 32MB RAM and 512MB HD. For the semiempirical calculations the CHEM-X [5] implementation of MOPAC 6.0 [6] was used. The transition state was searched with routines incorporated in MOPAC

[7]. The obtained saddle-point structure was optimized by NLLSQ which usually led to the transition-state structure. The optimized transition state was verified by performing frequency and thermal analyses at 130°C [8]. The structures of the starting point, the intermediate and the product were also fully optimized and the same vibrational and thermal analyses were performed.

The ab initio calculations [9] were performed with GAUSSIAN 92 [10] for WINDOWS. The search for saddle points in the reactions were performed only at the STO-3G and RHF levels. Otherwise, the stationary point structures obtained by PM3 calculations (reactant, first transition state, intermediate, second transition state and product) were used as input files for building the Gaussian Z-matrix.

The modeling of chemical reactivity and regioselectivity in cycloadditions [11] depends critically on the reliability of the underlying molecular orbital methods. As far as ab initio calculations for transition structures of pericyclic reactions are



Scheme 2. Proposed mechanism of transformation of the tetrazole molecule 1 into the oxadiazole 6 via two intermediates and three transition states.

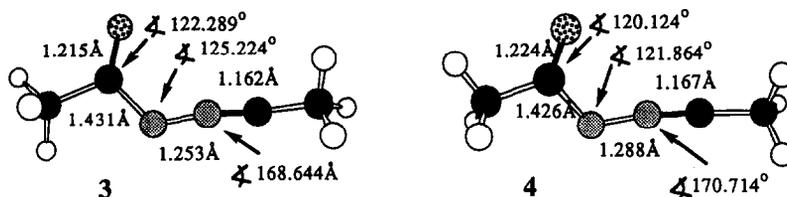


Fig. 1. The structural characteristics of two possible intermediates 3 and 4 calculated by PM3.

concerned, Houk et al. [12] have provided an analysis of different methods. A general discussion of ab initio and semiempirical procedures is given by Feller and Davidson [13] and Stewart [14] respectively.

3. Results and discussion

The proposed mechanism of the transformation of 2-acetyl-5-methyltetrazole (**1**) into 2,5-dimethyl-1,3,4-oxadiazole (**6**) is presented in Scheme 1. As is shown, two kinds of intermediates can be formed; one is a biradical (**3**) and the other has separated charges — the positive charge is located mostly on the carbon atom and the negative charge on the oxygen atom (**4**). Both species were optimized by AM1 [15] and PM3 [16]. The same input file was used for optimization of the structure of the intermediates, except in the case of **3** the keyword BIRADICAL was added. Both methods prefer the formation of the polar intermediate **4** over the biradical **3** (in the case of the PM3 calculation this difference is $6.5 \text{ kcal mol}^{-1}$). The calculated energy difference is reflected in the structural properties of these two intermediates (Fig. 1). Although there are small differences in the bond lengths and angles, they are quite similar. It is also possible that these structures are interconvertible, and probably a low energy barrier exists between them. Our attempt to

calculate this transition state with MOPAC failed. Because of the energy preference, we accepted the polar structure **4** as the intermediate of the reaction.

One major advantage of computational chemistry is the ability to calculate the structures on the reaction coordinate surface which cannot be determined experimentally [16]. The semiempirical calculations of the first transition state (T_1) that represents the transformation of reactant **1** into intermediate **4** (Scheme 1) are presented in Fig. 2. The structure of T_1 is quite similar for different MOPAC semiempirical methods. The most symmetrical are the AM1 and MINDO/3 structures, the newly formed bond difference being 0.106 Å in both cases, whereas the most asymmetrical is the structure generated by MINDO where $\Delta r = 0.264 \text{ Å}$.

The stepwise transformation of **1** into **6** via at least three transition states was also considered (Scheme 2). A saddle search was performed by submitting structures **1** and **7**, and **7** and **4**, respectively. Two saddle points that represent the third transition state (T_3) and the fourth transition state (T_4) were obtained by AM1 and MINDO/3. The saddle structures were then refined and were confirmed to be true transition states by obtaining only one imaginary vibration. The structures of the transition states obtained by MINDO/3 are presented in Fig. 3. The heats of formation of all the discussed species, by both the

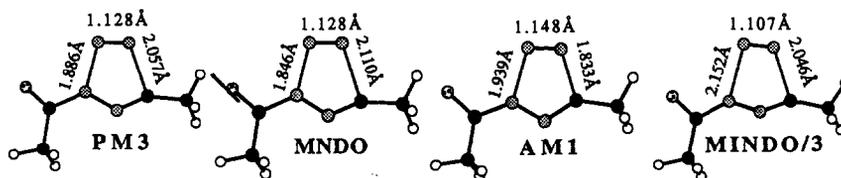


Fig. 2. The structures of T_1 calculated with MOPAC.

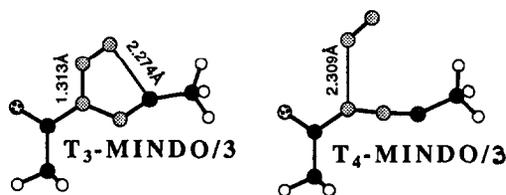


Fig. 3. Structures of the transition states T_3 and T_4 calculated by MINDO/3.

concerted and stepwise mechanisms, calculated by using the four semiempirical methods, are given in Table 1.

To resolve the problem of different mechanisms of the reaction we carried out the transition state calculation with ab initio methods. The structures of the first transition states are presented in Fig. 4. If we do not consider the conformational changes in the acetyl group, it can be concluded that the ab initio calculation prefers the concerted mechanism for elimination of the nitrogen molecule. Overall, the comparison of the structures obtained by semiempirical and by ab initio calculations suggests that the highest degree of similarity was observed between PM3 and 3-21G/6-31G. The two breaking bonds have slightly shorter lengths in the higher level ab initio calculations. The transition states are also asymmetrical but now the N–N distance is larger than the C–N distance. One should be aware that in the process of elimination of the

nitrogen molecule, a triple bond is formed. In such cases the inclusion of correlation energy is important and usually the energy obtained is somewhat lower than the one obtained at the Hartree–Fock level.

Both ab initio transition structures were used to build input files for AM1 and MINDO/3 NLLSQ optimization of the transition states. The resulting transition states were very similar to those presented in Fig. 2. This supports the fact that AM1 and MINDO/3 do not favor the synchronous mechanism of elimination of the nitrogen molecule from **1** but prefer the three-step mechanism presented in Scheme 2.

The second transition state (T_2) shows much greater similarity between different semiempirical and ab initio calculations. When optimization of T_2 was performed with NLLSQ the structure was very similar to intermediate **4**. To overcome this problem, the BIRADICAL keyword must be used. This suggests that the transition state might have biradical properties. The structures of T_2 calculated in this manner with different MOPAC methods are presented in Fig. 5. Although the C–O bond distance varies considerably from method to method, the same transition state is generated.

To confirm the structural features of T_2 calculated by semiempirical methods, it was

Table 1
Heats of formation (kcal mol^{-1}) of all species considered in both the concerted and stepwise mechanisms

Reactant	Concerted mechanism					Stepwise mechanism		
	T_1	N_2	3	4	T_2	T_3	T_4	
PM3	39.22	78.41	11.56	28.99	22.51	41.03	95.89	59.01
MNDO	3.78	77.51	8.28	38.74	28.98	40.32	83.61	50.15
AM1	76.80	116.06	11.16	47.10	39.77	50.86	110.57	60.65
CINDO/3	-89.64	-28.36	6.97	-50.03	-54.11	-28.20	-47.25	-42.44

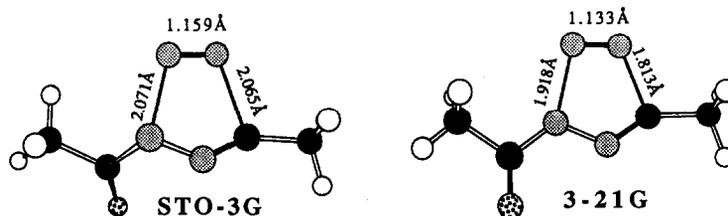


Fig. 4. Structures of the first transition state calculated by GAUSSIAN 92.

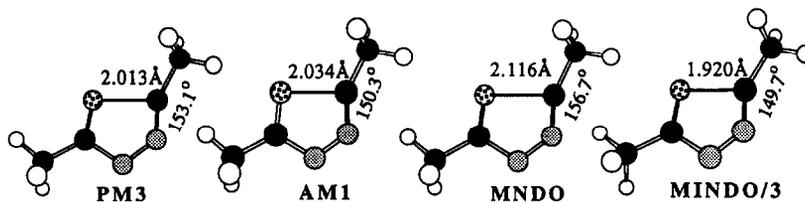


Fig. 5. The structure of the second transition state obtained by various methods from MOPAC.

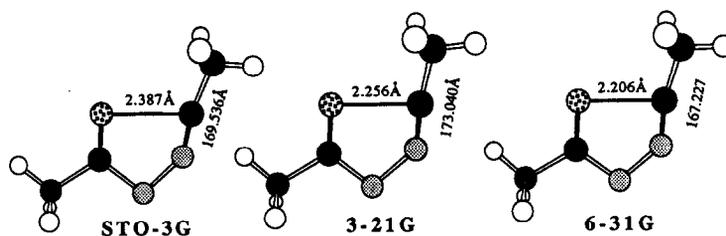


Fig. 6. The structure of the second transition state obtained by different levels of Gaussian calculations.

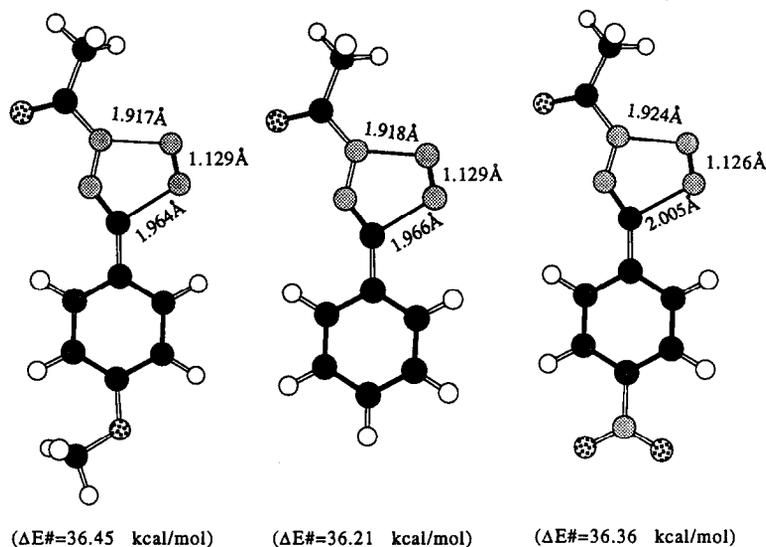


Fig. 7. The first transition state and the activation energies of some aromatic derivatives of 2-acetyltetrazole.

submitted to ab initio calculations. The structures of T_2 obtained by HF/STO-3G, HF/3-21G and HF/6-31G are presented in Fig. 6. Again the structure obtained by MINDO/3 is the one that differs the most from the Gaussian structures. Overall, the greatest similarities exist between the higher levels of ab initio calculations and the structures obtained by MNDO and PM3. It is quite conceivable that for the handling of organic anions, PM3 and MNDO can give comparable

results to the HF/6-31G level at a lower computer cost.

The calculation of the vibrational and thermal properties of the reactant, intermediate, product and the two transition states reveals that the activation energies at standard temperature (25°C) are 56.67 kcal mol⁻¹ for T_1 and 36.5 kcal mol⁻¹ for T_2 calculated by the PM3 method (if a biradical intermediate is assumed to be formed, the second energy barrier is

30.02 kcal mol⁻¹). Relatively small activation barriers are in agreement with our findings that acyltetrazoles are extremely reactive species.

To test the nature of the substituents on the tetrazole ring on the rate of the reactions, several 5-phenyl derivatives were studied with PM3 as the best semiempirical method for this type of reaction. Because T₁ has a higher activation energy, only the thermodynamic quantities were calculated on the reactants and the first transition states for p-nitrophenyl, phenyl and p-methoxyphenyl derivatives. The structures of their first transition states and activation energies are presented in Fig. 7. It is conceivable that the substituents on the aromatic ring of 2-acetyl-5-phenyltetrazole do not have a profound influence on the activation energy. This is in agreement with our experimental observation that substituents on the aromatic ring do not change the time necessary for completion of the reaction. It seems quite possible that the first transition states do not have highly polar character. However, we do not have experimental evidence that can support formation of the radical-like second transition state except that the calculation of the second transition state with MOPAC is only possible if the BIRADICAL keyword is used [17]. The second transition state has enough similarity to the one obtained with higher level ab initio calculations and we can, with some degree of confidence, say that the second transition state is well represented by PM3 calculations.

4. Conclusion

It has been shown that semiempirical methods can predict two different mechanisms of transformation of 2-acetyl-5-methyltetrazole into the corresponding oxadiazole. PM3 and MNDO are in agreement with results obtained by GAUSSIAN 92 calculations and prefer the elimination of nitrogen from the tetrazole ring by a synchronous mechanism. AM1 and MINDO/3 favor a three-step mechanism — first breaking the C–N bond and then the N–N bond in the elimination of the nitrogen molecule. The structure of the second transition state of the transformation of the intermediate into the oxadiazole is quite similar

for all the methods studied. It is also quite conceivable that the substituents do not have a profound influence on the rate of the reaction.

5. References

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