

Rates of hydrolysis of *N*-acetylazoles: semiempirical calculations compared to experimental values

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(Received 27 May 1993; accepted 8 July 1993)

Abstract

An investigation of the reactivity of *N*-acetylazoles was performed by AM1 semiempirical method. The calculated electronic and geometry properties of *N*-acetylazoles and azolium anions were in good correlation with the reactivity of the azoles. The transition state geometries of hydrolysis for *N*-acetylazoles were located and optimized. The activation energies were calculated and were used for evaluation of the rate of the hydrolysis and were in good agreement with experimental values.

Introduction

Derivatives of azoles as reactive intermediates have unique application in organic chemistry. Probably the most widely used of them all are the derivatives of imidazole [1,2]. The main reason why derivatives of imidazole have found such broad application is their modest reactivity, making them suitable for manipulation in a number of organic synthetic schemes. Recently, Katritzky and co-workers introduced derivatives of benzotriazoles as very useful reactive intermediates for preparation of a wide variety of precious organic compounds [3]. Nevertheless, derivatives of tetrazoles, the most prominent of all azoles, have seen little investigation [2,4]. Tetrazoles have several attractive features as intermediates. They are highly acidic [5] with pK_a 's comparable to carboxylic acids and they can be easily removed from the product with base extraction. The four nitrogen atoms can be bound covalently to a sub-

strate or their metal complexes [6] where one or two other nitrogen atoms are involved can selectively bring the substrate to the reactant. The major "disadvantage" is their high reactivity that can produce many undesirable side products. Nevertheless, we have been able to prepare *N*-acyltetrazoles [7] and *N*-alkyltetrazoles [8] in relatively high yield and have demonstrated their usefulness as intermediates for preparation of many desirable compounds. Their ability to make the complexes with transition metals [8] was useful for the study of chiro-induction that is ongoing in our laboratory. Tetrazoles are inexpensive and can be obtained in kilogram scales from available nitriles and sodium azide [9]. Furthermore, their reactivity can be adapted to the reaction which needs to be performed. Since it is well known that the acidity of benzoic acid can be altered by ring substituents [10], the reactivity of 5-phenyltetrazoles can be tailored in the same way by synthesizing them from substituted benzonitriles [8].

These facts encouraged us to study the reactivity of azole derivatives by semiempirical calculations. As small molecules the *N*-acetylazoles [11] were selected for three approaches as reported herein,

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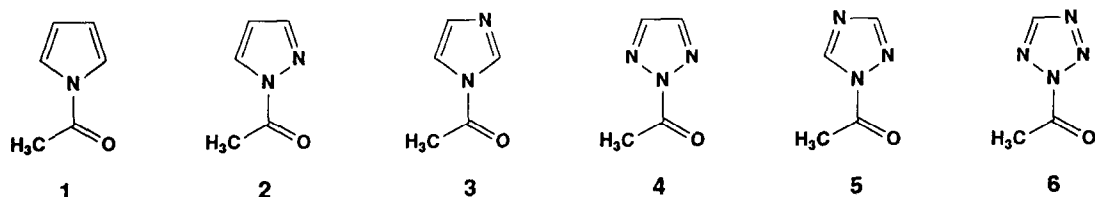


Fig. 1. Structures of the *N*-acetylazoles studied.

the calculation of the geometry and electronic properties of the reactant (*N*-acetylazole), the geometry and electronic properties of the leaving group (azolium anion), and the transition states were located so as to obtain the rates of hydrolysis.

Methods

The semiempirical computations were performed with MOPAC using the AM1 force field option [12]. MOPAC was run both on a DEC 7620 and on an IBM compatible 486 PC as part of the ChemX computational package [13]. ChemX was mainly used as a graphic interface, as well as for conformational searches and MM2 optimizations.

The Hückel energies were obtained by single point extended Hückel calculations with the HyperChem computational package [14].

The location of the transition state was also calculated with GAUSSIAN 92 [15] on a Silicon Graphics Personal Iris computer.

Results and discussion

The structures of *N*-acetylazoles studied are

presented in Fig. 1. Compounds 4, 5 and 6 exist in different isomeric forms – the ones presented were selected because of the available experimental data.

AM1 semiempirical calculations of N-acetylazoles and azolium anions

Prior to any semiempirical calculation all structures were submitted to MM2 energy optimization followed by conformational search. Two structures with the acetyl group and the heterocycle group in one plane for 2, 3, 5, and 6 and one structure for 1 and 4 were selected. All of them were submitted for geometry optimization with the AM1 semiempirical force field. The one with lowest energy was used for calculation of the electronic properties. Table 1 presents the AM1 calculated properties of the *N*-acetylazoles.

In the reaction of nucleophilic addition of water to *N*-acetylazole the water molecule is the electron donor while the azole molecule is the electron acceptor. The rate of reaction depends on the relative strength of both the donor and the acceptor. That was confirmed in our case by

Table 1
Calculated properties of *N*-acylazoles

Compound No	Atomic charges			Bond Length (Å)		LUMO (eV)
	N	C	O	C-O	C-N	
1	-0.18	0.32	-0.31	1.2400	1.4057	-0.0313
2	-0.19	0.34	-0.22	1.2373	1.4267	-0.1529
3	-0.21	0.32	-0.30	1.2386	1.4077	-0.2718
4	-0.18	0.35	-0.25	1.2305	1.4567	-0.3336
5	-0.22	0.35	-0.30	1.2405	1.4289	-0.4890
6	-0.25	0.36	-0.28	1.2346	1.4323	-0.9529

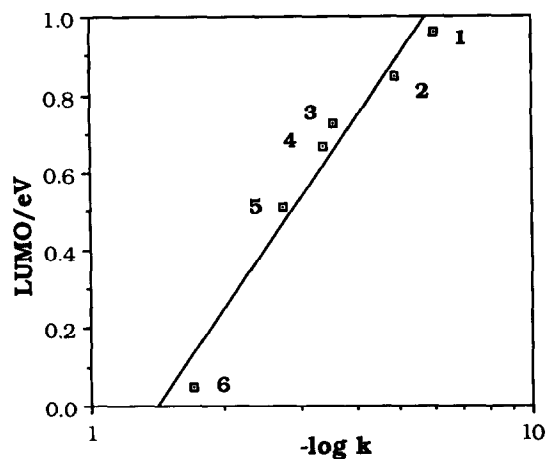


Fig. 2. Plot of LUMO energies vs. negative logarithm of the rate of hydrolysis.

relatively good logarithmic correlation (correlation coefficient = 0.957) of the LUMO energies of *N*-acetylazoles with the logarithm of their rate of hydrolysis (Fig. 2) [11].

The reactivity of *N*-acetylazoles depends upon their ability to accept the reactant water molecule. The nucleophilic water molecule will add to the carbonyl group and as such not only is the charge on the carbonyl carbon an important factor but also the charge separation between carbon and oxygen of the carbonyl group. The

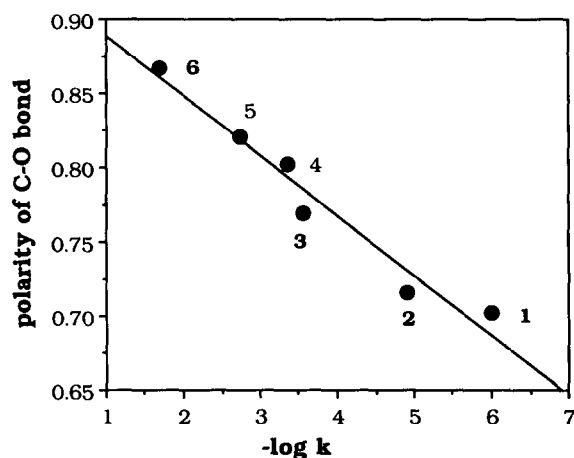


Fig. 3. Plot of polarity of carbonyl bond vs. negative logarithm of the rate of hydrolysis.

best determination of that ability is the polarity of the C-O bond calculated by multiplication of charge differences with the distance between two of these atoms. Although we are aware that the calculated atomic charges are not real values, they can help in the qualitative correlation of the *N*-acetylazoles reactivity. From the good correlation between C-O bond polarity and the negative logarithm of *N*-acetyl hydrolysis (correlation coefficient = 0.957) again one can predict the high reactivity of *N*-acetyltetrazoles (Fig. 3).

The third factor affecting the reactivity of the *N*-acetyltetrazole is the stability of the leaving groups, or azolium anion, as it is known that the reactivity of the substrate depends on the nature of the leaving group [16]. In order to determine the aromaticity of the leaving group we chose to compare the Hückel energies. To our disappointment the calculated Hückel energies of the leaving groups do not correlate very well (correlation coefficient only 0.917) with the negative logarithm of the rate of the hydrolysis of *N*-acetylazoles (Fig. 4). This can be explained by the fact that calculations were performed on structures in the gas phase, although it is known that the stability of the leaving groups strongly depends on interactions with solvent [17]. Nonetheless there is an obvious general trend.

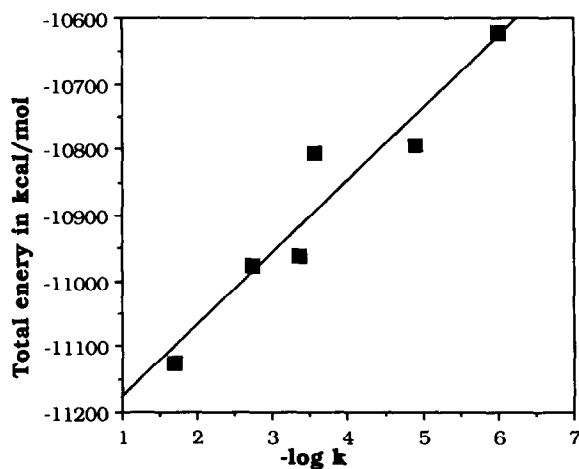
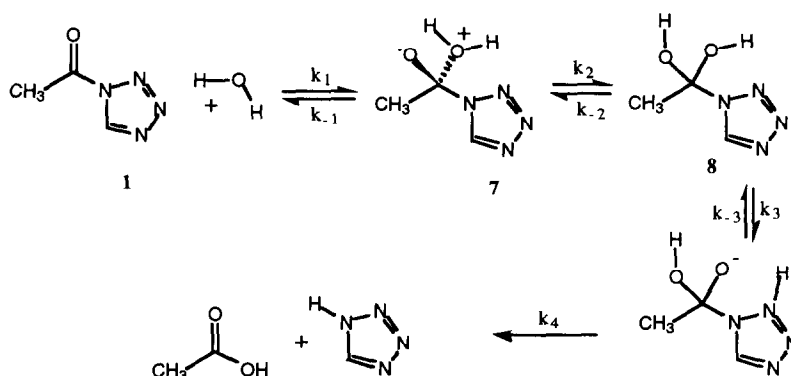


Fig. 4. Correlation of stability of leaving group with the rate of the hydrolysis of *N*-acetylazoles.



AM1 semiempirical calculations of transition state and rate of hydrolysis of N-acetyltetrazoles

The proposed mechanism of hydrolysis of N-acetyltetrazoles 1–6 is shown in Scheme 1 with N-acetyltetrazole as the model. We assume that the first step is rate determining and involves the addition of water to the carbonyl group of N-acetyltetrazole with the formation of tetrahedral intermediates 7 and 8. The mechanism is similar to the hydrolysis of esters proposed by Bender [18] and confirmed by him [19] and others [20].

For the reaction profile, three basic points on the potential surface were chosen for optimization. The first minimum corresponds to the reactants – water plus N-acetyltetrazoles – and the second minimum corresponds to the reaction intermediate 8 (intermediate 8 was chosen because the energy and the structure of intermediate 7 is too similar to the transition state and we had problems locating the transition state between reactants and 7). The third minimum is the intervening saddle point corresponding to the first transition state. The use of semiempirical methods for predicting a potential surface requires characterisation of these three points. The heat of formation of the two minima (reactants and the intermediary) was minimized by the modified Broyden–Fletcher–Goldfarb–Shamo method [21–24]. The transition state was located by performing a saddle calculation (SADDLE, XYZ keywords).

In the calculation of the reactants, the oxygen of water was placed 3.5 Å perpendicular to the carbonyl group (carbon). With this information, the program can optimize the geometry of the reactants, then the intermediate and from these two geometries proceed to a common middle point, i.e. the “transition state” [25].

The saddle calculations were executed until the saddle point had passed which was indicated by a reversal in gradient direction. The saddle point geometry (common structure) was then selected for the non-linear least squares gradient minimization routine (with keywords in the input file AM1 NLLSQ XYZ T=100H GNORM=0.0). The validity of the “transition state” was checked by performing vibrational analyses (keywords FORCE LET). If only one imaginary mode with an imaginary frequency (around -1980 cm^{-1}) with contribution from O–H–O ($\approx 95\%$) and O–C–O ($\approx 5\%$) vibration was generated, the geometry was subjected to further optimization. Otherwise the procedure was repeated with more carefully designated coordinates for the reactant and the intermediate.

The geometry that passed the test of vibrational analysis was subjected to conformational search for minimal energy without optimization of the structure. The C–N bond was rotated every 10° and a single point MM2 calculation together with AM1 NLLSQ analysis was performed [26]. The conformer with the minimal energy from the

Table 2
The experimental and AM1 calculated rates of hydrolysis of *N*-acetylazole

Compound	Experimental $k \times 10^5(\text{s})$	Calculated $k \times 10^5(\text{s})$
1	≈ 0	0.68
2	1.27	6.25
3	28.1	2.49
4	43.5	65.2
5	180	65.0
6	2000	1400

MM2 and NLLSQ methods were selected and further refined by the McIver-Komornicki gradient norm minimization routine (keyword SIGMA). This minimization routine gives better correlation with experimental results.

Two points are important for calculation of rate of the hydrolysis: the fully optimized reactants and the fully optimized transition state. The vibrational partition function calculations were performed for both of them, for the reactants that are 3.5 Å apart the calculations were performed with keywords FORCE THERMO(298,298) ROT=1, whereas in the case of the transition state an extra LET keyword was added. The rate constants were then

calculated using the formula

$$k = (RT/h)_{\text{ex}}(-V_0/RT)(Q_{\text{vib}}^{\ddagger}/Q_{\text{vib}})$$

where R is the gas constant ($\text{cal K}^{-1} \text{mol}^{-1}$), T the temperature (K), V_0 the activation energy (cal mol^{-1}), $Q_{\text{vib}}^{\ddagger}$ the transition-state vibrational partition function, Q_{vib} the ground-state vibrational partition function. The transitional partition functions cancel and the contributions of the rotational partition functions were very small compared to the vibrational partition functions and their influence to the calculated rate is negligible. Table 2 presents relatively good agreement between experimentally and AM1 obtained results. Only one rate constant of hydrolysis is about ten times lower than the experimentally obtained value. This can be explained by the strong influence of hydrogen bonding between N3 of the imidazole ring and the water molecule which makes the substrate much more reactive. For example, this phenomena is very well known in the enzymatic hydrolysis with the imidazole group present in the active site of the enzyme [27].

We tried introducing a second water molecule with the sole purpose of making the hydrogen bond with the "free" nitrogens of the azole ring.

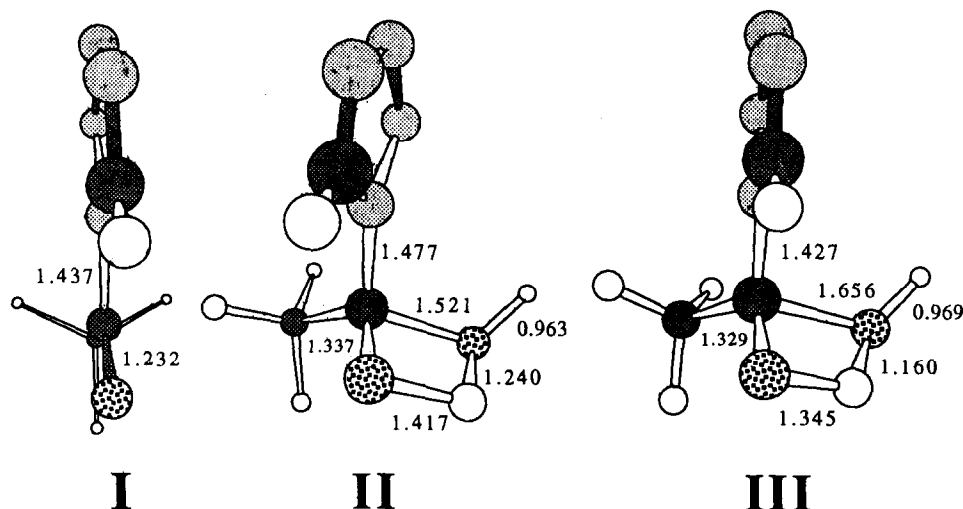


Fig. 5. AM1 MOPAC generated structures of the *N*-acetyltetrazole (I) and its hydrolysis transition states obtained by AM1 MOPAC (II) and GAUSSIAN 92 (III).

The search for the transition state and the proceeding conformational analysis was much more complex than with only one water molecule. In this way the rate of hydrolysis of *N*-acetylimidazole was slightly improved ($3.1 \times 10^{-5} \text{ s}^{-1}$) [28].

The AM1 structures of *N*-acetyltetrazole as the most reactive compound in the series studied here and its transition state is presented in Fig. 5. It can be observed that in the transition state calculated by both semiempirical AM1 and ab initio methods the length of the carbonyl (C–O) bond is between that of a single and double bond and one water hydrogen lies somewhere between water oxygen and carbonyl oxygen while the other water hydrogen makes a hydrogen bond with the closest nitrogen atom. Although the same transition state calculated with these two methods differs in the bond lengths the energy differences are negligible ($0.25 \text{ kcal mol}^{-1}$). Similar structural features of the transition state for 1–5 *N*-acetylazoles were observed.

Conclusion

We have demonstrated that the results obtained by AM1 semiempirical calculations of electronic properties as well as the rate of hydrolysis of the *N*-acetylazoles are in close agreement with their experimentally obtained reactivity. These observations together with our and other experimentally obtained results strongly support the application of reactive tetrazole intermediates in organic syntheses.

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