HETEROCYCLIC REARRANGEMENTS. - A SEMIEMPIRICAL STUDY OF A DEGENERATE REARRANGEMENT IN THE 1,2,4-OXADIAZOLE SERIES

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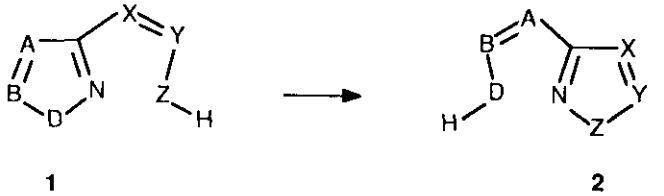
Abstract - A semiempirical approach to the degenerate rearrangement of the 3-acetylamino-5-methyl-1,2,4-oxadiazole is reported. Quantum mechanical calculations at the MNDO and AM1 level have been carried out for the anionic form of the acetylaminooxadiazole and for the transition state. The theoretical value of activation energy for the degenerate process has been compared with the experimental free energy of activation previously obtained by the dynamic ^{1}H-nmr. The calculations have been also extended to the different conformers of the anionic acetylamino moiety and to the conformational processes. Furthermore, a quasi-degenerate rearrangement for the 3-trideuterioacetylamino-5-methyl-1,2,4-oxadiazole has been pointed out by nmr technique, and the calculated free energy of activation confirmed the expected lower reactivity of the neutral species with respect to the anionic one.

INTRODUCTION

Heterocyclic rearrangements of five membered rings involving the participation of three side chain atoms are well documented in literature.[1] According to the Boulton-Katritzky Scheme 1 ⟶ 2 ,[2] they cover the azole to azole interconversions,[3] also named and reviewed[1a] as "mononuclear heterocyclic rearrangements".

Among these reactions, 3-acylamino-1,2,4-oxadiazoles (**3**) and (**4**) have furnished interesting examples of thermally induced rearrangements of the *iso*-heterocyclic type,[4] which can be also degenerate[5] when R = R^1. In particular, 3-benzoylamino-5-methyl-1,2,4-oxadiazole (**3**; R = Me, R^1 = Ph) and the corresponding 3-acetylamino-5-phenyl-1,2,4-oxadiazole (**4**; R = Me, R^1 = Ph) have been shown to give a thermally induced equilibrium process where the 5-phenyl-substituted oxadiazole was the significantly favoured component.[4] On the other hand, the potassium salt of 3-acetylamino-5-methyl-1,2,4-oxadiazole (**5**) showed in the nmr spectrum [$(CD_3)_2SO$] two methyl singlets, reversibly coalescing at 112°C; from the coalescence temperature and the frequency separation of methyl singlets, a value of free energy of activation, $\Delta G^{\neq}$, of 19.6 kcal mol^{-1} was calculated.[5] However, for the neutral species (**5**), no coalescence phenomenon was observed up to 190°C in $(CD_3)_2SO$, thus indicating for the hypothetic reversible process a $\Delta G^{\neq}$ higher than 25 kcal mol^{-1}.

Scheme 1



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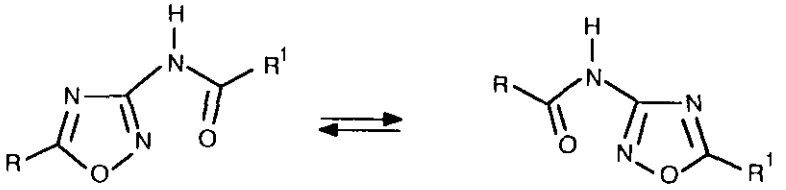
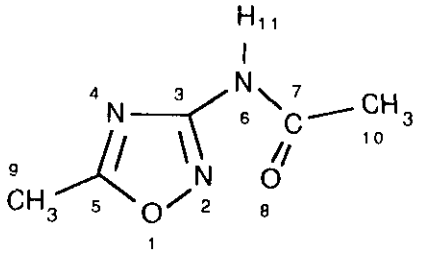


3 **4**

Recently, some of us have focused their attention to the photochemical behaviour of 3-acylamino-1,2,4-oxadiazoles, aiming to a photochemical approach to the *iso*-heterocyclic processes.[6] Moreover mechanistic investigations on this class of heterocyclic rearrangements have been widely reported.[7] Now, in connection with our interest in the five membered ring chemistry and in order to have more insights into the *iso*-heterocyclic

rearrangements of 1,2,4-oxadiazole systems, we became interested in a theoretical approach to this special class of thermally induced rearrangements.[8] In this connection we decided to analyse these reactions by means of semiempirical quantum mechanical calculations, in order to estimate activation parameters and the structure of the transition state. In this paper we report results concerning the thermally induced rearrangement of the anion (**6**); moreover, in order to estimate the importance of the conformational isomerism of the acetylamino group in the coalescence phenomenon, we have extended the theoretical treatment to different conformers of the anionic acetylamino moiety, *e.g.*, **7** and **8**, and to the corresponding conformational processes.

Scheme 2



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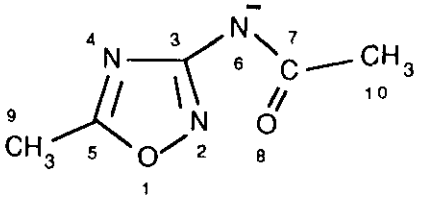

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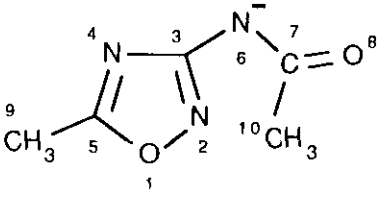

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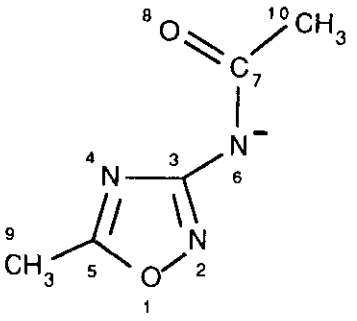

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METHOD OF CALCULATION

Molecular orbital calculations have been carried out at the MNDO and AM1 semiempirical level by using the AMPAC program.[9] Molecular geometries of the studied systems have been fully optimized in a planar arrangement (except for hydrogen atoms of methyl groups). As regards the conformational isomerism, we have optimized the geometries of the anions (**7**) and (**8**) derived from **6** through a rotation by 180° of the acetylamino group around the N(6)-C(7) bond or the C(3)-N(6) bond, respectively.

For obtaining the structure of the transition state for the anionic degenerate rearrangement we have performed a series of minimizations as functions of the O(1)-N(2) distance (the assumed coordinate reaction). In the case of the conformational isomerism, the reaction coordinate has been taken as the dihedral angle C(3)-N(6)-C(7)-C(10) for the process **6** ⟶ **7** and the dihedral angle N(4)-C(3)-N(6)-C(7) for the process **6** ⟶ **8**, respectively. Of course, the choice of the coordinate reaction is in some manner arbitrary, so we outline that the obtained structures of the transition states are an approximation to the *true* transition states.

RESULTS AND DISCUSSION

Bond lengths and bond angles of the anion (**6**) and the transition state for the degenerate rearrangement are reported in Table 1; calculated energy values as well as the resulting values of the activation energies are shown in Tables 2 and 3.

Considering the degenerate rearrangement of the anion (**6**), the main difference in going from the starting system to the transition state is observed in the values of bond angles of the pentatomic ring. This means that this part of the molecule, through relevant modifications of the bond angles, allows a relatively facile course of the reaction. Moreover, the transition state geometry is characterized by a different length between the O(1)-N(2) bond being cleaved and the N(2)-O(8) bond being formed, *i.e.*, by an asymmetrical arrangement in the coordinated reaction.

Regarding the energetic aspects of the rearrangement, theoretical calculations give a value of 71.6 kcal mol^{-1} in the case of MNDO calculation and 47.6 kcal mol^{-1} in the case of AM1 hamiltonian as the difference in the total energy between the anionic species (**6**) and the transition state. Since the rearrangement occurs without a significant change in the

Table 1. Calculated bond lengths (Å) and bond angles (degrees) for structure (**6**) and for the transition state (T.S.).

	6		T. S.	
	MNDO	AM1	MNDO	AM1
O(1)-N(2)	1.310	1.326	2.2	2.2
N(2)-C(3)	1.375	1.387	1.349	1.355
C(3)-N(4)	1.431	1.472	1.389	1.423
N(4)-C(5)	1.330	1.321	1.372	1.361
C(5)-O(1)	1.369	1.418	1.259	1.281
C(3)-N(6)	1.344	1.362	1.360	1.384
N(6)-C(7)	1.376	1.366	1.382	1.372
C(7)-O(8)	1.243	1.261	1.244	1.262
N(2)-O(8)	3.010	2.950	2.789	2.771
C(5)-C(9)	1.493	1.473	1.520	1.505
C(7)-C(10)	1.534	1.527	1.530	1.522
C-H (average)	1.110	1.116	1.109	1.116
O(1)-N(2)-C(3)	107.4	107.5	92.1	88.6
N(2)-C(3)-N(4)	108.6	108.6	117.7	121.9
C(3)-N(4)-C(5)	103.7	103.9	115.5	113.5
N(4)-C(5)-O(1)	111.1	111.2	120.9	121.9
C(5)-O(1)-N(2)	109.2	108.8	93.8	94.1
N(4)-C(3)-N(6)	118.3	119.0	116.0	115.4
C(3)-N(6)-C(7)	125.3	122.3	123.9	121.8
N(6)-C(7)-O(8)	127.8	129.5	126.2	128.6
N(4)-C(5)-C(9)	128.3	132.6	116.8	119.2
N(6)-C(7)-C(10)	111.7	113.7	112.4	114.0

Table 2. Transition state search for the anionic degenerate rearrangement (energy values in kcal mol^{-1}).

MNDO method O(1)-N(2) bond length (Å)	total energy	N(2)-O(8) bond length (Å)
1.310	-69.2	3.016
1.4	-64.4	3.004
1.6	-37.8	2.961
1.8	-13.0	2.904
2.0	0.0	2.835
2.1	2.1	2.812
2.2	2.4	2.789
2.3	1.6	2.772
2.4	0.5	2.755
2.6	-1.1	2.738
2.8	-68.0	1.311

AM1 method O(1)-N(2) bond length (Å)	total energy	N(2)-O(8) bond length (Å)
1.326	-13.3	2.950
2.1	33.4	2.784
2.2	34.3	2.771
2.3	33.7	2.758

	$\Delta E^{\neq}$ (kcal mol^{-1})
MNDO	71.6
AM1	47.6

Table 3. Transition state search for the conformational processes (energy values in kcal mol^{-1}).

Dihedral angle (degrees) C(3)-N(6)-C(7)-C(10)	Total Energy	
	MNDO	AM1
180	-69.2	-13.3
100	-65.4	-6.9
90	-65.2	-6.8
80	-65.1	-7.1
70	-65.1	
60	-65.1	
50	-65.1	
40	-65.3	
0	-66.3	-12.8
Dihedral angle (degrees) N(4)-C(3)-N(6)-C(7)		
180	-69.2	-13.3
110	-66.5	-10.5
100	-66.3	-10.3
90	-66.3	-10.3
80	-66.5	-10.5
0	-69.2	-13.6

	$\Delta E^{\neq}$ (6 → 7)	$\Delta E^{\neq}$ (6 → 8)
MNDO	4.1	2.9
AM1	6.5	3.0

volume of the substrate, it seems reasonable to suppose that the activation entropy may be expected to have a negligible role. Therefore, we can compare the experimental value of the free energy of activation (19.6 kcal mol^{-1}) with the calculated energy change of the involved species. It is evident that there is a marked difference between experimental and theoretical values, especially in the case of MNDO result. However, our opinion is that this difference could be due to the fact that the experimental value is obtained in solution: the dipolar aprotic solvent should favour dramatically the interconversion process in the anionic species as generally observed[1a,5,10] for these type of heterocyclic rearrangements, thus lowering the corresponding activation energy.

With regard to the conformational isomerism of the anionic acetylamino group, theoretical calculations allows us to observe that there are negligible differences in the total energies between rotational isomers (**6**), (**7**), and (**8**), so that it is impossible to assign a preferred conformation to the isolated anion. Nevertheless, whichever the preferred conformation may be, undoubtedly the difference in energy between the starting conformer and its rotational transition state is too low to be compared with the value calculated for the rearrangement process. Therefore, on the basis of MO calculations we can exclude that the coalescence phenomenon may be due to the rotational isomerism around the amide bond in the anionic species.

These conclusions being drawn, we next focused our attention to the possibility of providing experimental evidence of a *quasi*-degenerate rearrangement in a neutral species in order to estimate the corresponding activation parameters. With this in mind, we have looked at the 3-trideuterioacetylamino-5-methyl-1,2,4-oxadiazole (**9**). For this compound, the expected *quasi*-degenerate rearrangement into an equimolar mixture containing both 3-trideuterioacetylamino-5-methyl (**9**) and 3-acetylamino-5-trideuteriomethyl-1,2,4-oxadiazole (**10**) could have been followed by ^{1}H-nmr measurements on the basis of the forecast different field of methyl signals for **9** and **10**.

When we reacted 3-amino-5-methyl-1,2,4-oxadiazole with deuterated acetic anhydride in refluxing benzene, we obtained an equimolar mixture of **9** and **10** (nmr analysis), thus indicating that the rearrangement occurred in the reaction conditions. However, when we performed the acetylation reaction by using the trideuterioacetylchloride in the presence of pyridine in benzene at room temperature, we isolated the expected trideuterioacetylamino derivative (**9**) containing some amounts (about 12%) of the corresponding isomer (**10**).

Since it was impossible to have a pure sample of compound (**9**), we used this enriched mixture for a kinetic investigation.

Scheme 3

9 **10**

The *quasi*-degenerate rearrangement process was followed by the ^{1}H-nmr technique in $(CD_3)_2SO$ at three different temperatures, and the concentration (%) of the components (**9**) and (**10**) was determined by integrating methyl singlets at δ 2.50 and δ 2.10, respectively. The kinetic constants were obtained by an A $\rightleftharpoons$ A' equilibrium reaction treatment,[11] and a value of the free energy of activation, $\Delta G^{\neq}$, of 27 kcal mol^{-1} was then calculated. In the figure we report the characteristic plot of the concentration (%) of compound (**10**) *versus* time in the rearrangement of compound (**9**) at 60.0°C in $(CD_3)_2SO$.

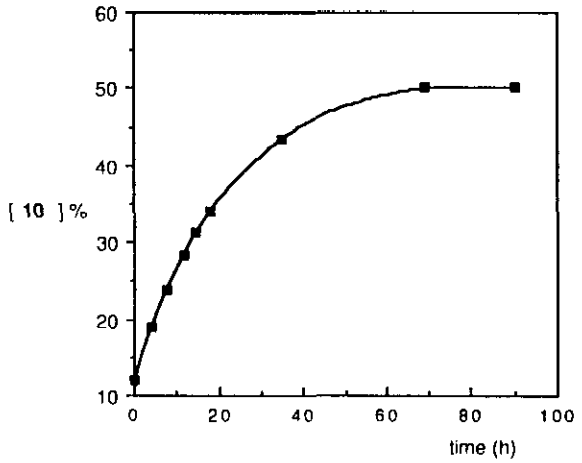

Figure. Plot of the concentration (%) of compound (**10**) *versus* time in the rearrangement of compound (**9**) at 60.0°C in $(CD_3)_2SO$.

As expected on the basis of the previous comments, the experimental value of the free energy of activation for the *quasi*-degenerate rearrangement of the neutral species, is higher than that obtained for the anionic species by the coalescence phenomenon; this result agrees with the higher reactivity of an anionic side chain sequence in a mononuclear heterocyclic rearrangement.

EXPERIMENTAL

^{1}H-Nmr spectra (60 MHz) were recorded on a Varian EM 360 spectrometer (tetramethylsilane as internal standard).

Reaction of 3-Amino-5-methyl-1,2,4-oxadiazole with Trideuterioacetyl Chloride.

To a suspension of 3-amino-5-methyl-1,2,4-oxadiazole (1 g, 10 mmol), in anhydrous benzene (100 ml) containing pyridine (1 g, 12 mmol), the trideuterioacetyl chloride (1 g, 12 mmol) was added and the mixture was kept at room temperature for 40 h. Evaporation of the solvent under reduced pressure gave a residue which was worked up with water and then extracted with chloroform. Evaporation of this solvent gave a residue (1 g, 70%) which was taken up with benzene and filtered off giving the mixture of compounds (**9**) and (**10**) (0.9 g, 62%), mp 163°C (from benzene)(lit.,[4] mp of 3-acetylamino derivative **3**, 163°C); ^{1}H-nmr [$(CD_3)_2SO$] δ: 2.10 (s, 3H, CH_3) (**10**; 12%), 2.50 (s, 3H, CH_3) (**9**; 88%), 11.0 (s, 2H, NH) (**9** + **10**).

Kinetics Measurements.

A sample of compound (**9**) (200 mg) in $(CD_3)_2SO$ (2 ml) was portioned in three nmr probes which were kept at 40.0°C, 50.0°C, and 60.0°C, respectively, and then used for the registration of the nmr spectra. Integration of the methyl singlets at δ 2.50 for compound (**9**) and δ 2.10 for compound (**10**) allowed to calculate the concentration (%) of the mixture components *versus* time. The thermodinamic parameters, calculated by using the kinetic treatment relative to the A $\rightleftharpoons$ A' equilibrium reaction,[11] were: k [s^{-1}] = 5.8×10^{-7} (40.0°C); 1.9×10^{-6} (50.0°C); 6.7×10^{-6} (60.0°C); $\Delta G^{\neq}$ = 27 kcal mol^{-1}.

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