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MNDO Study of the Boulton–Katritzky Rearrangement

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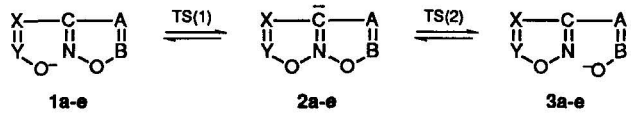
An MNDO study of the title rearrangement has shown that the reaction proceeds in a non-concerted manner *via* an unstable bicyclic intermediate.



a; A = N, B = CH, X = N, Y = CH
b; A = B = X = Y = CH
c; A = CH, B = N, X = CH, Y = N
d; A = B = X = CH, Y = N
e; A = N, B = X = CH, Y = N

Scheme 1

Recently, we have studied theoretically the Boulton–Katritzky rearrangement by the MNDO method using the AMPAC suite of programs.[1] When our investigations were complete a communication describing an MNDO study of such a rearrangement of 3-acetamido-5-methyl-1,2,4-oxadiazole appeared in the press.[2] Taking into account the difference between our data and those obtained in ref. 2, we decided to publish the preliminary results of our study.

The Boulton-Katritzky rearrangement is known to be base-catalysed. Therefore, calculations were made for the anionic derivatives **1a–c** (which for this rearrangement are degenerate) and also for the anions of the 3-hydroxyiminomethyl derivatives of isoxazole **1d** and 1,2,4-oxadiazole **1e** (Scheme 1). The enthalpies of formation of the initial, intermediate and final molecules and transition states are presented in Table 1.

In our investigations, the distance between the ring nitrogen atom and the terminal oxygen atom of the side chain was considered as the reaction coordinate. A study of the isomerization mechanism and a determination of the approximate geometry of the transition state were carried out using the reaction coordinate method so that all internal coordinates were optimized completely for the fixed N—O distance. La Manna *et al.*[2] proceeded from an assumption that molecular planarity was preserved during the rearrangement. We have established that the approach of the N and O atoms up to a distance of 2.0 Å does not destroy the planarity, but when this distance becomes less than 2.0 Å the planarity is distorted: the molecule becomes folded along the C=N bond. As a result, the ring carbon atom becomes pyramidal. The transition state of the reaction has an unsymmetric structure and is achieved at an N—O distance of 1.61–1.69 Å. The values of the bond lengths and valency angles for the transition state of the degenerate rearrangement of 1,2,4-oxadiazole derivative **1a** are presented in Fig. 1. In this state the initial ring remains almost planar and

Table 1 Enthalpies of formation of initial, intermediate and final molecules and transition states for the Boulton–Katritzky rearrangement of heterocyclic anions **1a–e**[a]

Compound	ΔH_f/kcal mol^{-1}[b]				
	1	TS(1)	**2**	TS(2)	**3**
a	−49.9	22.4	10.0	22.4	−49.9
b	−43.8	35.3	23.3	35.3	−43.8
c	5.8	63.8	49.8	63.8	5.8
d	−11.1	49.1	35.0	49.0	−27.9
e	−18.0	42.0	30.0	42.9	−27.6

[a] See Scheme 1. [b] 1 cal = 4.184 J.

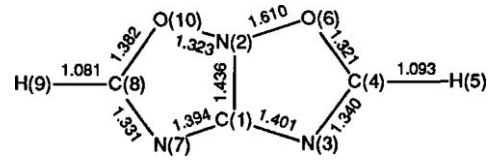


Fig. 1 Transition state for the Boulton–Katritzky rearrangement of the anion of 3-formamido-1,2,4-oxadiazole, slowing calculated bond lengths (Å). Valence angles (°): N(2)C(1)N(3) 112.7, N(2)C(1)N(7) 110.1, N(3)C(1)N(7) 125.8, C(1)N(3)C(4) 104.6, N(3)C(4)H(5) 121.7, H(5)C(4)O(6) 120.9, N(3)C(4)O(6) 117.4, C(4)O(6)N(2) 104.2, C(1)N(7)C(8) 103.6, N(7)C(8)H(9) 128.2, N(7)C(8)O(10) 112.4, H(9)C(8)O(10) 119.4, C(8)O(10)N(2) 109.0, C(1)N(2)O(6) 98.9, C(1)N(2)O(10) 104.9, O(6)N(2)O(10) 123.4

the dihedral angle O(10)N(2)C(1)N(7) is 3.3°. At the same time, the atoms of the newly formed ring strongly deviate from planarity and the dihedral angle O(6)N(2)C(1)N(3) is 14.6°. As a result, nitrogen atom N(3) leaves the plane of the C(1)N(2)O(10)C(8)N(7) heterocyclic ring. The dihedral angle O(10)N(2)C(1)N(3) is reduced from 180° in the initial anion to 145.9° in the transition state. That the structure obtained corresponds to the transition state is confirmed by the fact that only one force constant having a negative sign was obtained for this structure.

Further shortening of the N—O distance leads to a bicyclic structure (in the case of the degenerate rearrangement this structure is symmetric) corresponding to the energy minimum on the potential curve. A calculation on the reverse process (splitting of the bicyclic intermediate during the lengthening of the N—O bond) shows that the reaction proceeds *via* the same route. The angle between the planes of the two heterocyclic rings is about 130–135° in the bicyclic intermediate **2**. The bridgehead nitrogen atom is pyramidal, the C—N bond is practically single, with a length of 1.50–1.52 Å. The negative charge is localized mainly on the carbon atom. Thus, the results of the calculations demonstrate that the reaction occurs in two steps in a non-concerted manner.

The calculated values of the activation barriers are considerably higher than those obtained experimentally.[3] In our opinion, the reason for this difference is that the experimental values were obtained for a reaction carried out in solution, whereas it is known that polar solvents considerably reduce the activation energy of rearrangements of this type.[2,3]

In contrast to our study, the authors of ref. 2 took the distance between the ring nitrogen and ring oxygen atoms as their reaction coordinate. However, our calculations showed that the approach of the cyclic nitrogen and acyclic oxygen atoms up to the formation of the intermediate was accompanied by an insignificant change of the ring N—O bond length (about 0.05 Å). This choice of reaction coordinate did not allow these authors to determine the true route for the rearrangement. The sudden change in the molecular energy (by almost 70 kcal mol^{-1}) and the molecular geometry observed after the achievement of the transition state provide evidence that the obtained route was erroneous. Also, as the reaction under study is a degenerate one, it must proceed *via* a symmetrical structure corresponding either to the transition state or to the intermediate. However, according to the previous results,[2] the reaction had only one stage and proceeded *via* an unsymmetrical transition state.

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