HETEROCYCLES, Vol 19, No 1, 1982

HYDROGENOLYTIC CLEAVAGE OF C=O BOND IN γ-PIPERIDONE DERIVATIVES

Waleria Wysocka

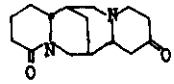
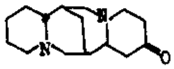
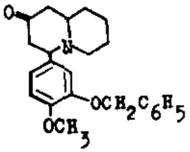
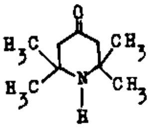
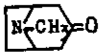
Institute of Chemistry, A. Mickiewicz University, Poznań, Poland

Abstract - The proton transfer via the hydrogen bond system of γ-aminoketones, dissolved in aqueous solution of strong acids, is postulated as the driving force for the hydrogenolytic cleavage of the C=O bond of γ-piperidone derivatives.

Investigation on the stereochemistry of the catalytic reduction of the keto group in cyclic six-membered γ-aminoketones has shown that the reduction by catalytic hydrogenation in neutral medium, in the presence of platinum (Adams's catalyst) proceeds easily and stereoselectively to the alcohols,[1,2] while in the aqueous solution of strong acids, the keto group undergoes facile transformation into the gem-diols.[3] Formation of such gem-diols was observed by means of the spectroscopic methods: ^{13}C nmr, ir, uv[3] as well as by the circular dichroism studies.[4] Some of the gem-diols were isolated as the stable hydrochloric salts.[3] Under appropriate acidic conditions the hydrogenolysis proceeds in 100% yield.[3] The amount of catalyst as well as the type of anion (e.g. ClO_4^-) does not influence the reduction-hydrogenolysis products ratio.[2] The hydrogenolysis reaction proceeds without passing through the intermediate alcohol stage, since the amino alcohols (reduction products) are not hydrogenolyzed when treated under the same conditions.[1] The facile hydrogenolysis of the keto group without forming intermediate alcohol suggests, that this process is assisted by the positively charged nitrogen which transannularly affects the γ-carbon.[1-3] The hydrogenolysis rate of the γ-aminoketones depends upon the ability of the molecule to adopt the most favourable conformation for this above-mentioned interaction. Such a type of interaction would be efficient only when the six-membered ring can adopt the boat conformation in which both interacting groups are most closely situated.[3] The conformational transformation of the piperidine ring of the γ-aminoketones into a boat form was ascertained by means of the ^{13}C-nmr spectra.[3] The reaction time and the products of hydrogenolysis of the various γ-aminoketones are given in the Table.

Table

Results of Hydrogenolysis of γ-aminoketones

Compound Hydrogenated	Hydrogenolysis Time h	Specificity for Hydrogenolysis Products % a)	
		2N HCl	6N HCl
	3	100	
	3	80	100
	3	60	95
	12	90	100
	40	100	
	40	100	
	40	100	
	35b)	20	100

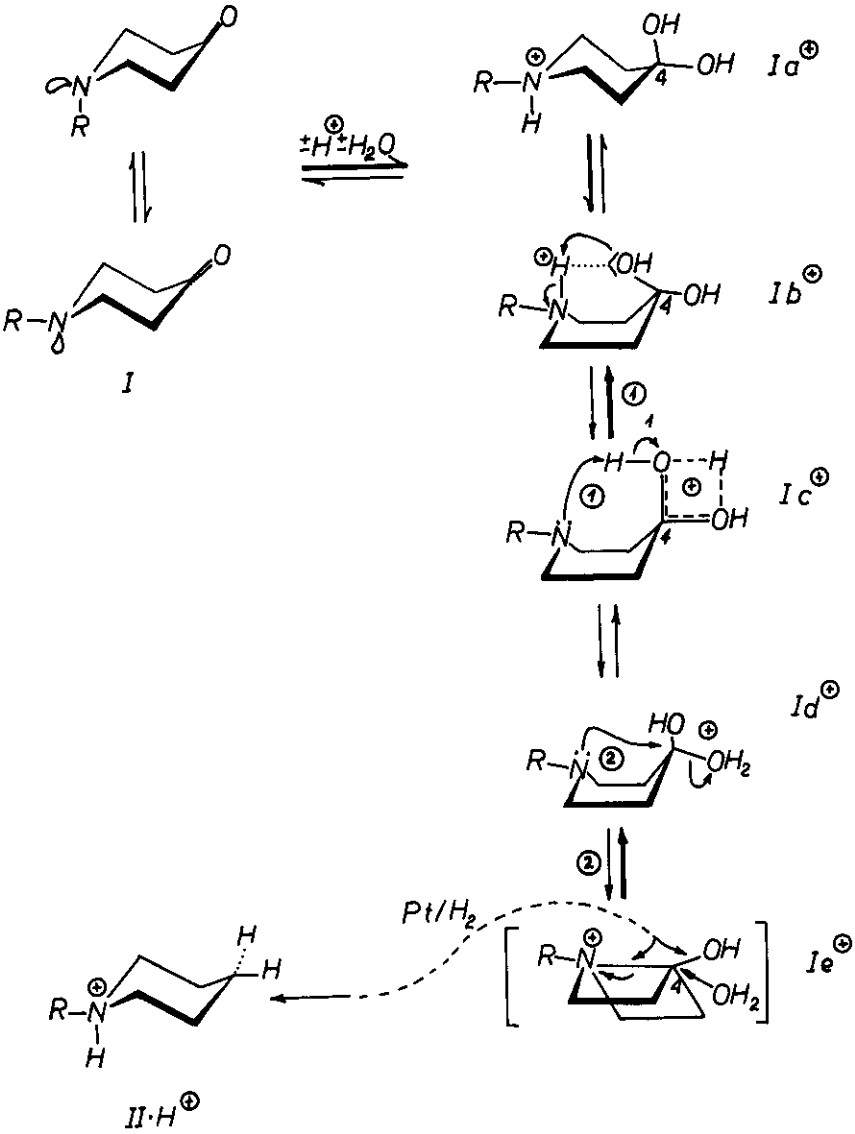
General conditions: 0.3 g of aminoketone and 0.03 g of platinum dioxide (Anachemia Industries, Montreal, Canada) in 10 ml of hydrochloric acid at 0.002 atm hydrogen pressure in a simple glass apparatus.

a) Isolated products characterized by ir, nmr, and ms spectra as well as by the elemental analysis.

b) According to Louis P. Reiff and Herbert S. Aaron (Tetrahedron Letters, 1967, **24**, 2329), 100% yield was achieved in 6N HCl at 50 psig hydrogen pressure for 3 h in a Parr Hydrogenator.

The data in the Table show that the hydrogenolysis of the keto group in simple γ-aminoketones system proceeds at the slowest rate due to the less stable boat conformation of the piperidine ring of these ketones. The methyl groups in position 1 or 2,2 and 6,6 of these compounds do not influence the reaction time.
To gain more precise insight into the hydrogenolysis mechanism, the reaction was also carried out in methanolic solution saturated with dry hydrogen chloride. As it could be predicted,[5] under these reaction conditions hemiketals are formed, but these hemiketals do not undergo any further transformation. When the reaction was carried out in methanolic solution at 2 - 6 molar ratio of $HClO_4$ and the aminoketones, formation of 1 - 5% hydrogenolysis product was observed (the formation of the gem-diols was caused by water contained in 70% $HClO_4$).
^{13}C-nmr spectra of the γ-aminoketones in 1-2N DCl solution showed a double amount of the signals for all carbons, due to the dynamic state of equilibrium between individual tautomers formed (Scheme, Ia$^+$ - Ie$^+$). The natural consequence of this equilibrium seems to be the formation of a hydrogen bond between the N$^+$-H group and the oxygen of axial hydroxyl of the gem-diol group. This kind of hydrogen bond is considered to be rather a weak one.[6] However, the presence of the easily polarizable hydrogen bond in the aqueous reaction medium causes the polarizability of the originally non-polarizable hydrogen bond [7] N$^+$-H...OH(a). Assuming a very fast prototropy and the later elimination of the water molecule (Scheme Ib$^+$ $\rightleftharpoons$ Ic$^+$ $\rightleftharpoons$ Id$^+$) followed by the quaternization of the nitrogen (Ie$^+$), the formation of the carbinolammonium cation (Ie$^+$) can be reasonably suggested as shown in Scheme. The very active quasi-covalent bond generated between the nitrogen and the γ-carbon in Ie$^+$ can be easily hydrolized, leading to the mixture of tautomers: Id$^+$, Ic$^+$, Ib$^+$. It can be assumed that in the active cation (Ie$^+$) under the conditions of catalytic hydrogenation (Pt-H_2), both the N-C and C-OH bonds undergo hydrogenolytic cleavage, leading to the methylene group (II - H$^+$).
The above consideration leads to the assumption that the transfer of the proton via the hydrogen bond system of the gem-diols in aqueous solution in the presence of strong acid is the driving force for the discussed hydrogenolysis process.[8] Consequently, it is assumed that the disruption of such a proton transfer via hydrogen bond system should retain such a reaction. In the case of reaction carried out in methanolic solution saturated with dry hydrogen chlori-

de, resulting in the formation of the hemiketals, one may expect a disruption of proton transfer. In consequence no hydrogenolysis is observed.



This work was supported by the Polish Academy of Sciences in the framework of problem No. MR-I.9.2.2.

References and Notes -

1. W. Wysocka and M. Wiewiórowski, Bull. Acad. Polon. Sci., Soc. Sci. Chim., 1974, 22, 831.
2. W. Wysocka, ibid., 1976, 24, 275.
3. W. Wysocka, ibid., 1980, 28, 263.
4. W. Wysocka and J. Gawroński, J. Chem. Soc. Perkin I, 1979, 8, 1948.
5. W. Wysocka, Bull. Acad. Polon. Sci., Soc. Sci. Chim., 1980, 28, 19, A. F. Casy. Experientia, 1964, 20, 437.
6. L. P. Kuhn, R. A. Wires, W. Puoft and H. Kurt, J. Amer. Chem. Soc., 1969, 91, 4790.
7. G. Zundel "Hydratation and Molecular Interaction", Academic Press, New York, London, 1969, R. Janoschek, E. G. Weidemann, H. Pfeiffer and G. Zundel, J. Amer. Chem. Soc., 1972, 94, 2387; R. Janoschek, E. G. Weidemann and G. Zundel, J. Chem. Soc. Faraday II, 1973, 69, 505.
8. The hypothesis agrees with the Blow assumption that the active mechanism of enzymes is due to the proton transfer via the hydrogen bond system in enzymes. See D. M. Blow, J. J. Birkteoft and B. S. Hartley, Nature, 1969, 221, 337.

Received, 20th July, 1981