Chemistry of Natural Compounds, Vol. 29, No. 5, 1993

A QUANTUM–CHEMICAL INVESTIGATION OF DEOXYPEGANINE AND ITS SALTS

II. THE PHOTOCHEMICAL OXIDATION OF DEOXYPEGANINE HYDROCHLORIDE

Kh. N. Aripov, Kh. R. Ashirmatov, Kh. R. Nuriddinov,
and L. V. Molchanov

UDC 541.6:547.7:856

The stability of deoxypeganine hydrochloride under the action of light has been established. The kinetics of the oxidation of deoxypeganine hydrochloride in aqueous solution in the presence of deoxyvasicinone hydrochloride have been studied. The structures and electronic conformations of hypothetical models of the salt DOP HCl in the ground and excited states have been considered by the MO LCAO method in the AM1 approximation. The difference in the resistance of the molecules of the base deoxypeganine and its hydrochloride to photochemical oxidation is discussed on the basis of the results of experiments and calculations.

The oxidation of quinazoline alkaloids to the corresponding quinazolones hs been reported by many workers [1-4]. Previously, using DOP as an example, the experimental facts on photochemical oxidation were investigated by quantum–chemical calculations, the mechanism of oxidation was substantiated theoretically, and the influence of the nature of the solvent on the rate of oxidation was established. It was found that oxidation is most intensive in aprotic solvents [3, 4]. A check on the oxidation of a 1% solution of DOP HCl in water over a long period under the action of daylight showed the absence of the oxidation product - DOV HCl. However, the presence of DOV HCl as an impurity in the DOP HCl solution destabilizes the system, inducing the oxidation of the DOP HCl under the action of light. It must be mentioned that the oxidation of DOP HCl depends on the pH of the aqueous olution: in strongly acid media when the pH is below 1.8 no oxidation takes place even in the presence of DOV HCl molecules. The titation curve of the the base DOV with hydrochloric acid solution showed that in aqueous solutions the salt DOV HCl undergoes hydrolysis, and the pH of a 0.1 M solution of DOV HCl titrated to an equimolar ratio is 2.35.

The oxidative process in aqueous solutions of DOP HCl was studied in diffuse room light. The change in composition was monitored by HPLC analyses over four months, the change in the pH of the solution being determined simultaneously [5]. At 20-25°C the oxidative process began when the level of DOV HCl in the DOP HCl was greater than 0.5%. A rise in the temperature of the medium led to a fall in this limit to 0.3%. Figure 2 gives the oxidation curves of two model solutions, each containing 1.0% of DOP HCl, with 1.1% of the salt DOV HCl as impurity in the first case and 3.0% of the base DOV in the second case. The initial pH values of these solutions were 3.55 and 6.55, respectively. It can seen from the angles of slope of the oxidation curves that the rate of oxidation was higher where the impurity in the DOP HCl was the base DOV. After relatively rapid photooxidation for some time (about 20 days) the process slowed down. In the region of the inflection in the kinetic curve, simultaneously with a decrease in the rate of oxidation there was a fall in the pH of the solution, which showed the occurrence of active hydrolysis of the DOP HCl under the action of the DOV and a rapid oxidation of the free DOV by a mechanism described previously [4]. The establishment of oxidative equilibrium depends on the concentration of DOV.

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*Abbreviations: HPLC) high-performance liquid chromatography; MO LCAO) molecular orbitals as linear combinations of atomic orbitals; AM1) Austin Model 1; DOP HCl) deoxypeganine hydrochloride; DOV HCl) deoxyvasicinone hydrochloride.

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 729-733, September-October, 1993. Original article submitted Februry 9, 1993.

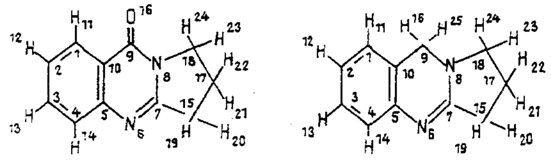

Fig. 1. The numbering of the atoms of the DOV (I) and DOP (II) molecules.

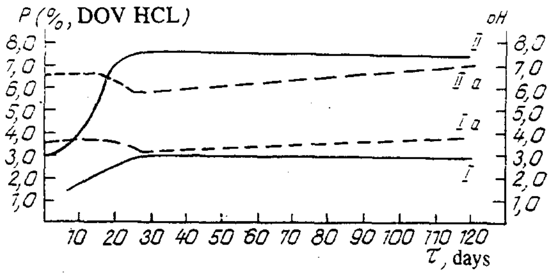

Fig. 2. Curves of the photooxidation of DOP HCl containing 1.10% of DOV HCl as an impurity in H_2O at pH 3.55 (I — %; Ia — pH) and with 3% of DOV at pH 6.55 (II — %; IIa — pH).

Thus, in the pure form, the DOP HCl molecule, unlike that of the base DOP is not oxidized on photosensitization. To find the reason for the stabilization of the DOP molecule in the process of salt formation we carried out a quantum-chemical investigation of possible hypothetical models of the bond of HCl with DOP in the ground and the excited triplet states.

It had been shown by earlier calculations for the base DOP that photooxidation takes place at the C_9 center, since in aprotic solvents in the excited triplet state a low electron density is retained at this center and the bonds of C_9 with H_{16} and H_{25} are considerably weakened As a result of the action of light quanta an autooxidation process takes place [4].

Calculations performed for hypothetical models of deoxypeganine hydrochloride in the excited triplet state (Fig. 3) have shown that only in case (VIII), when the bond with HCl is at N_8, is an increase in the electron density at C_9 observed (the magnitude and sign of the charge on the the C_9 atom on passing from the molecule of (II) to (VIII) changes from 0.03 to −0.01, Fig. 3) and this center becomes proton-accepting, in contrast to the other models, in which the C_9 atom remains nucleophilic, as in the unexcited molecules. At the same time, in the ground state, another important characteristic of the molecules — the energy of the interatomic bonds between the C_9 and the H_{16} and H_{25} atoms —, which, like the charge on the atoms, helps to explain the mechanism of the photooxidative process, remains practically unchanged on passing from one model to another. In comparison with the excited molecule of the base DOP (II), the energies of the bonds of C_9 with H_{16} and H_{25} weaken only slightly in system (VII) (see Table 1). These two characteristics of the C_9 atom, namely the magnitude of the charge and the energies of the bonds, are the main limiting factors for the oxidative process. Thus, the $N_8-{}_9$ fragment of the DOP molecule becomes responsible for the stabilization or destabilization of the systems considered.

Usually the appearance of an ionic bond between the Cl^- anion and N_8-H^+ has been considered energetically unfavorable because of the steric influence of the neighboring atoms. However, a comparison of electron densities on the N_6 and N_8 atoms in the excited triplet state and the values of the heats of formation of the hypothetical models has shown that the probability of the migration of HCl from the N_6 to the N_8 atom increases, since N_6 in the excited triplet state becomes less proton-accepting, while the N_8 atom retains its own level of proton-accepting capacity. As a result, with a proton H^+ the N_8 atom gives a $-N_8H^+$ center capable of forming an ionic bond with Cl^-. Moreover, in the hypothetical models (IV) and (VI) the distributions of electron density and of the energy of the interatomic C−H bonds in the ground and excited triplet states differ little from the case of DOP in the form of the base, and, in these models the possibility of oxidation is retained. However, experiments have shown that, in the pure form, DOP HCl is not oxidized. Thus, in the excited triplet state the salt DOP HCl forms groups in aqueous solution through the protonation of N_8, since, because of photoexcitation and the passage of the molecule into the triplet state, the electron density of the whole conjugated system is delocalized and the conditions are created for the formation of a N_8H^+ ionic center, which, in its turn, stabilizes the N_8-C_9 fragment.

TABLE 1. Energies of the Bonds between the Atoms in the Ground and Excited States or the DOP HCl Molecule (in eV units)

Bond	I	II	III	IV	V	VI	VII	VIII
E(1—11)	12.56	12.53	12.56	12.53	12.55	12.52	12.56	12.53
E(2—12)	12.62	12.64	12.62	12.64	12.62	12.64	12.61	12.62
E(3—13)	12.57	12.58	12.57	12.57	12.56	12.58	12.57	12.57
E(4—14)	12.56	12.51	12.55	12.51	12.56	12.51	12.55	12.52
E(9—16)	11.96	11.74	11.96	11.73	11.96	11.73	11.96	11.83
E(9—25)	11.96	11.75	11.96	11.75	11.96	11.74	11.98	11.86
E_m(C—H)*	12.20	12.15	12.20	12.16	12.20	12.16	12.21	12.16
E(N—HCl)	—	—	0.40	0.23	—	—	0.37	0.20

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*For the polymethylene ring.

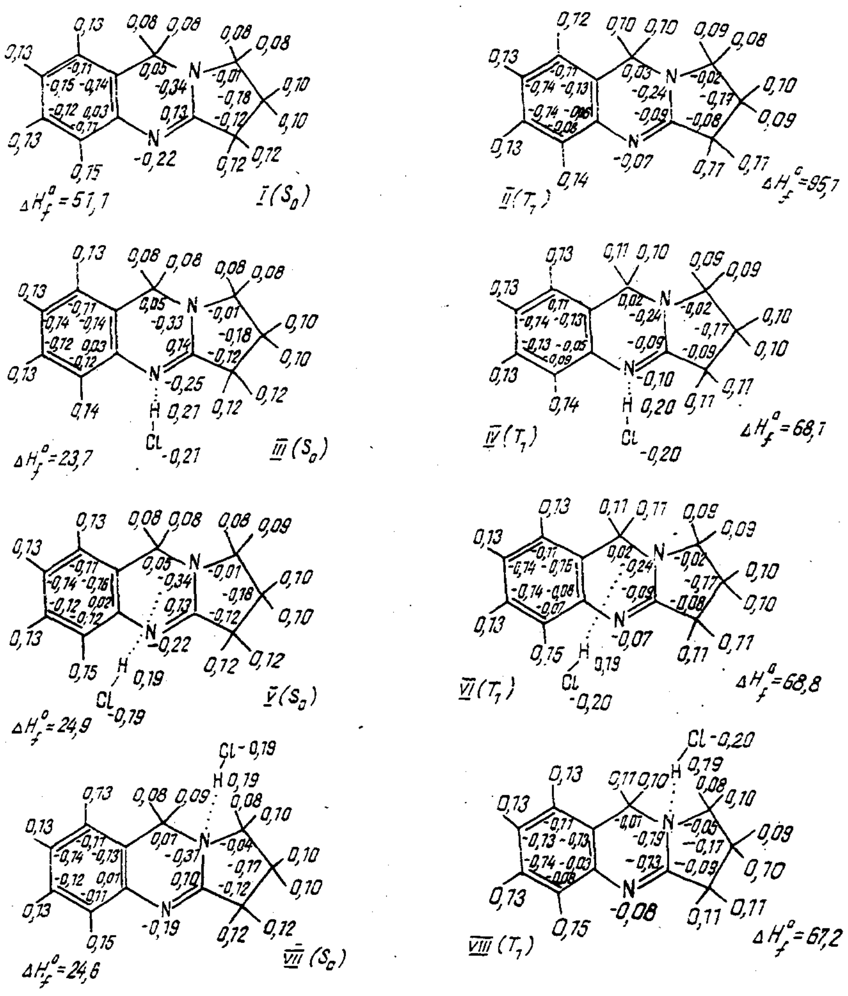

Fig. 3. Distribution of charges on the atoms and heats of formation of the DOP and DOP HCl molecules in the ground and excited triplet states (in e units and kcalmole, respectively).

A weighty argument in confirmation of the conclusion drawn and also of results on the structure and reactivity of DOP HCl is the energetic preferability of model (VIII) over others (II, IV, VI). Thus, on comparing heats of formation it can be seen that system (VIII) (the case in which the HCl counter-ion directly attacks the nitrogen atom of the "pyrrole" type above the plane) is preferable to models (IV) (the case in which the HCl counter-ion attacks the nitrogen atom of the "pyridine" type in the plane of the DOP skeleton) and (VI) (the case in which the HCl counter-ion attacks the heterocycle above the plane, being oriented to the center of the ring perpendicularly to the plane of the skeleton of the molecule) by 0.9 and 1.7 kcal/mole, respectively (Fig. 3). At the same time, in the cases of models (III, V, and VII), which correspond to the ground state, the most preferred model form of the of the molecule is that according to which the counter-ion attacks the "pyridine" nitrogen atom in the plane of the molecule (system (III) is preferable to (VII) and (V) by 0.9 and 1.2 kcal/mole respectively). Consequently, on the basis of a comparison of the heats of formation of molecules calculated by the AM1 method it may be asserted that the system most resistant to photooxidation and chemical oxidation is that in which HCl interacts with the N_8 atom (III), the HCl being oriented almost perpendicularly to the plane of the DOP skeleton. At the same time, in unexcited systems, that form is preferable in which the HCl binds to the N_6 atom (III). Consequently, in the excited state systems corresponding to model (VIII) predominate. The formation of salts corresponding to model (III) is characteristic for ordinary, unexcited, systems.

Thus, confirmation by quantum–chemical calculations of the experimental results on the resistance of DOP HCl to photooxidation has enabled the structure of the salt DOP HCl in the excited triplet state to be established.

It must be mentioned that in the triplet state, as a result of the delocalization of the electron density of the heterocycle (Fig. 3) the basicity of DOP falls and the N_6...HCl and N_8...HCl bonds in models IV and VIII are weakened (see Table 1), as a consequence of which in the presence of the impurity DOV HCl, which, as mentioned above, is highly hydrolyzed in aqueous solution, the exchange of a HCl molecule between the salt DOP HCl and the bse DOV is quite probable. As in the experiments described above, the result is that partial oxidation of the DOP HCl takes place. This theoretical conclusion on the initiation of the hydrolysis of DOP HCl is confirmed by the experimentally observed fall in the pH of the solutions in the period of the rapid oxidation of DOP HCl, with a subsequent rise in the pH to the original level after the cessation of the oxidative process. The results presented are of practical value, since they show that the anticholinesterase drug deoxypeganine hydrochloride must be not less than 99.5% pure after the reduction of DOV to DOP.

EXPERIMENTAL

The HPLC separation of DOP HCl and DOV HCl was conducted on a Milikhrom chromatograph using KAX-2 microcolumns (2 × 62 mm) with Separon-C18 (5 μm)). Isocratic elution was carried out with the eluant MeOH containing 0.1 M CH_3COONa and 0.4 M CH_3COOH, at the rate of 100 μl/min. The separation of the substances was monitored with a Milikhrom UV detector at 254 nm. The sensitivity of detection for DOV HCl was 5 ng (or 5 μg/ml). The volume of sample deposited on the column was 1 μl. The pH values of the solutions were measured with a pH-121 pH-meter.

The quantum–chemical calculations were conducted by the MO LCAO method in the AM1 approximation using the AMPAC program on a PC AT 386 [6]. The geometric parameters of the molecules in the ground and excited states were completely optimized.

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