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Synthesis, spectroscopy, computational study and prospective biological activity of two novel 1,3,2-diazaphospholidine-2,4,5-triones

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ABSTRACT

The preparation of two new 1,3,2-diazaphospholidine-2,4,5-triones is reported. Thus, 2-chloro-1,3,2-diazaphospholidine-2,4,5-trione [ClP(O)(NHC(O)C(O)NH) (**I**)] and 2-benzylamino-1,3,2-diazaphospholidine-2,4,5-trione [$C_6H_5CH_2NHP(O)(NHC(O)C(O)NH)$ (**II**)] have been synthesized by the reaction of $POCl_3$ with the corresponding carboxylic diamide salts. The characterization of the compound **I** was performed by multinuclear (^1H, ^{13}C, ^{31}P) NMR and FTIR spectroscopies, elemental analysis and also mass spectrometry. Both compounds show two signals at room temperature in the low field region of the ^1H NMR spectrum, which collapsed to a single peak when the temperature is increased. Dynamic NMR (^1H DNMR) and quantum chemical studies were performed to gain insight from this conversion process. The free activation energies, calculated at the coalescence temperatures are 18.51 and 17.45 kcal/mol for compounds (**I**) and (**II**), respectively, which are associated with a tautomeric interconversion process, most likely between the lactam and lactim forms. The relative energy, molecular geometry and vibrational properties of several plausible tautomers were analyzed by using quantum chemical calculations at the HF/6-311G** and B3LYP/6-311++G** levels of the theory. The nuclear magnetic shielding tensors have been calculated for both tautomeric forms using the gauge independent atomic orbital (GIAO) method at the B3LYP/6-311++G(3df,2p) level of approximation. A biological activity prediction using the PASS software shows that compound (**I**) can be characterized by a superb anti-HIV activity whereas compound (**II**) is a very good antineoplastic.

1. Introduction

N-heterocycles formed by oxo group(s) constitute a family of polar ligands with peculiar properties since they may change either their hydrogen-bond donating or accepting sites through the protonation/deprotonation process or by a tautomeric transformation. Pyrimidine and purine derivatives are the best-known examples for such oxo-hydroxy (lactam-lactim) tautomerism [1,2]. 3-OH and 5-OH isooxazoles also show this proton relocation mechanism [3–5]. Another important class of molecules with this versatility consists of five-membered heterocycles with at least two more N atoms in the ring. In the neutral form, N-atom is bounded to a mobile H-atom (pyrrolic N–H) whereas the remaining N-atoms posses a basic character being their lone pairs formally situated in the ring plane. Imidazole is the most well-known representative of this family [6–8].

The syntheses of heterocycles containing N- and pentavalent P-atoms (phospholidines) as well as carbonyl groups (Scheme 1) were conducted by Becke-Goehring and Wolf [9] reacting oxamide with PCl_5. In such a five-membered ring heterocycles, the reactivity of the heteroatom towards nucleophiles is greatly enhanced in comparison with the acyclic analogues. The reactivity of phospholidines towards amines and alcohols, as well as the mechanism and the influence of steric hindrance have been reported [10]. Moreover, the molecular structure for the 1,3-dimethyl-2-methylamino-1,3,2-diazaphospholidine-2,4,5-trione (Scheme 1) has been studied from an X-ray diffraction analysis [11].

Carbacylamidophosphate compounds with general formula $R'C(O)NHP(O)R_2$ have a decisive role in catalytic and metabolism processes [12–14], and many applications in agricultural and pharmacological industries [15–19]. Their rich biological activity is related with the presence of a peptide group in these compounds. Some *N*-ethyleneimine derivatives at the phosphoryl group have been proposed as anti-cancer drugs [20–22]. Furthermore, carbacylamidophosphate compounds are also potential O,O′-donor

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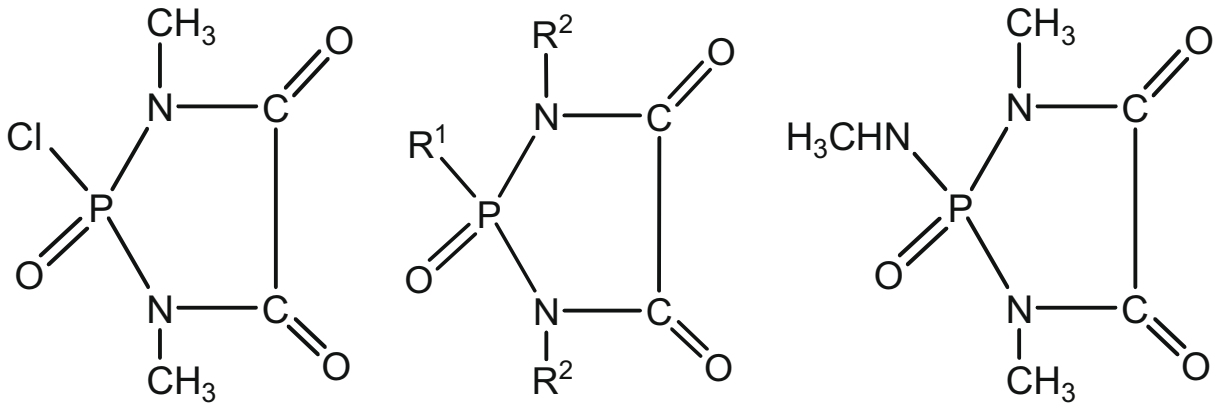

Scheme 1. Five membered heterocycles (phospholidines) related with the species studied in this work. *Left:* 1,3-Dimethyl-2-chloro-1,3,2-diazaphospholidine-2,4,5-trione [9]. *Centre:* 1,3-(R^2)-2-R^1-1,3,2-diazaphospholidine-2,4,5-trione, with (R_1 = Alk, OAlk, OAr, R_2 = Me, CH_2Ph) [10]. *Right:* 1,3-dimethyl-2-methylamino-1,3,2-diazaphospholidine-2,4,5-trione [11].

ligands for metal ions and play a dominant role as ligands in the development of transition metal-catalyzed asymmetric synthesis specially as powerful chelating systems, closely related to β-diketonates [23–25]. Carboxylamides have a very low nucleophilic reactivity on their nitrogen moieties due to the interaction between N-atom and the C=O π-system [26,27]. In addition, reactions of phosphorus halides with amides lead to products in which the contribution of the P–O linkage is more evident than the corresponding P–N linkages [12,26,27]. This wide range of applications has stimulated a great research effort involving preparations and characterizations of compounds possessing the –C(O)NHP(O)– moiety [22,23,28–36].

In the present study, two new cyclic diazaphospholidine species have been synthesized by the reaction of $POCl_3$ with the carboxylic diamide (oxamide) salt. The characterization of the products was carried out by IR, ^1H, ^{13}C, ^{31}P NMR spectroscopy, elemental analysis and also mass spectrometry for compound (**I**). Both compounds show two signals at room temperature in the low field region of the ^1H NMR spectrum, which collapsed to a single peak when the temperature is increased. Dynamic NMR (DNMR) and quantum chemical studies were performed to clarify this process. Moreover, a prediction of the biological activity for these compounds was performed using the PASS (prediction of activity spectra for substances) software [37–43].

2. Results

2.1. Synthesis

The synthesis of the compound **I** was carried out according to Eq. (1)

$$Na_2(H_2N_2C_2O_2) + POCl_3 \rightarrow ClP(O)(NHC(O)C(O)NH) + 2NaCl \quad (1)$$

A mixture of oxamide ($H_2NC(O)C(O)NH_2$) and NaH dissolved in toluene was stirred at ca. 110 °C. After 3.5 h, the mixture was filtered and the solvent was distilled off in vacuum. To the formed oxamide natrium salt in benzene was added a large excess of $POCl_3$ under stirring. After 6 h refluxing, the mixture was filtered and **I** was obtained in a yield of 83 %. All reactions were done under inert (dry gas N_2) atmosphere.

Compound **II** was subsequently prepared by reaction of **I** with benzyl amine according to Eq. (2)

$$ClP(O)(NHC(O)C(O)NH) + C_6H_5CH_2NH_2 \rightarrow C_6H_5CH_2NHP(O)(NHC(O)C(O)NH) + HCl \quad (2)$$

Compound **I** and benzyl amine were dissolved in chloroform at 0 °C and stirred for 5 h. The mixture was then filtered and the remaining solid was purified by washing with DMF and Et_2O. Compound **II** was obtained in a yield of 90%.

2.2. Mass spectrometry

Mass spectrum of **I** reveals the presence of the molecular ion at *m*/*z* 168. Its fragmentation shows two peaks at *m*/*z* 133 and 105, corresponding to the loss of Cl and ClC=O groups and three intense peaks at *m*/*z* 89, 59, 42 due to the P(O)NC=O, NPN and NC=O fragments, respectively.

2.3. NMR spectroscopy

^1H NMR spectra of the products show two signals corresponding to amidic H-atom at 7.68 ppm and 7.97 ppm for **I** and at 7.66 ppm and 7.92 ppm for **II**. In addition **II** shows typical signals corresponding to the aromatic ring and to the methylene group. As expected for compound **I**, the ^{13}C NMR spectrum shows only one single peak in the carbonylic region at 163.4 ppm assigned to the C=O group. For compound **II**, the ^{13}C NMR shows in addition peaks from the aromatic ring and the methylene moiety. In the ^{31}P NMR spectra both compounds present a signal near −0.8 ppm.

The peaks near 7.8 ppm in the ^1H NMR spectra disappear when compounds **I** and **II** are dissolved in D_2O. Whereas no changes are observed by decreasing the temperature of the aqueous solutions, both peaks collapse at higher temperatures. The coalescence temperatures (T_c) are 90 °C for (**I**), and 70 °C for (**II**) (Fig. 1).

2.4. Vibrational spectra

To our knowledge, no vibrational spectra for phospholidinones have been reported. The analysis of calculated harmonic vibrational frequencies can be useful in the present circumstances for both purposes, the assignment of the experimental vibrational data and the search for the occurrence of tautomeric forms (See Fig. 2). A tentative assignment of the observed bands was carried out by comparison with theoretical wavenumbers, as well as with relevant data reported in the literature for related molecules [45–47]. The main features in the vibrational spectra can be satisfactorily interpreted on the basis of the presence of one most stable oxo tautomer. Characteristic fundamental modes assigned to the vibrations of cyclic N-carbonyl phosphordiamidates moiety in compounds **I** and **II** are shown on Table 1.