Conformational, IR spectroscopic and electronic properties of conium alkaloids and their adducts with C_{60} fullerene

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ABSTRACT

Conformational, IR spectroscopic and electronic properties of the components of Conium alkaloids (*Conium maculatum*) in aqueous environment were determined by model calculations and experiment. With the help of FT-IR spectroscopy the possibility of formation of an adduct between γ-coniceine alkaloid and C_{60} fullerene was demonstrated, which is important for further application of conium analogues in biomedical purposes.

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1. Introduction

It is known that a significant number of modern drugs that are used in medicine are derived from herbal extracts [1]. Thus, the main herbal bioactive agents used to treat malignancies, are the alkaloids of piperidine group exhibiting pronounced cytostatic effect on tumor cells. However, antitumor chemotherapy demonstrates low efficiency in treatment of locally advanced and disseminated forms of malignancies. In this context, modification of pharmacological properties of already known antitumor agents with an aim to reduce their resistance and adverse side effects is considered as the promising approach on the way of developing new highly efficient antitumor drugs. A typical example of this strategy is a change of the structure and properties of active ingredient molecules through the formation of complexes with nanoparticles [2—7]. The molecular aggregates formed in this way are characterized by developing of specific biological activity and,

consequently, improved therapeutic properties [8—11]. In this context the use of C_{60} fullerene as a modifier of anticancer drugs seems a promising approach [10—14]. The idea is based on the fact that C_{60} molecule acts as an effective electron acceptor [15—17] due to the ability to induce charge transfer, or forms covalent adducts with standard drugs [3,18,19]. This factor can significantly affect the properties of drugs due to formation of stable complexes with them.

Another important feature of C_{60} fullerene is its ability to facilitate generation of singlet oxygen in biological tissues during UV/Vis irradiation [20—22]. It is known that the singlet oxygen in tumor tissue damages cell membranes and organelles, and causes their death. Another important issue is electronic and conformational characteristics of drug-fullerene complexes. Consideration of these parameters allows to predict activity of alkaloids and their adducts on interaction with cell components, which is commonly determined by the electrostatic forces [23].

Among the set of potential candidates for synthesizing new selective anticancer drugs, the conium (*Conium maculatum*) is considered to be a promising substrate, which includes such alkaloids as coniine ($C_8H_{17}N$), N-methylconiine ($C_9H_{19}N$), γ-coniceine ($C_8H_{15}N$), conhydrine ($C_8H_{17}NO$) and pseudoconhydrine ($C_8H_{17}NO$) [8]. Therefore, the purpose of the present work was: (1) to develop

a numerical model for appropriate description of conformational states of conium alkaloids in aqueous environment; (2) by means of FT-IR spectroscopy to testify the possibility of formation of an adduct between conium and C_{60} fullerene which may alter the biological activity of the former.

2. Materials and methods

The pristine C_{60} fullerene aqueous colloid solution (C_{60}FAS) in 0.15 mg/ml concentration of C_{60} fullerene used in the experiments, was prepared according to the protocols [24,25]. The conium solution (*Conium maculatum* D3, Weleda, Germany) in 0.15 mg/ml concentration was used.

The initial solutions of conium and C_{60}FAS were mixed in 1:1 volume ratio and the resulting mixture was treated for 30 min in the ultrasonic disperser.

For recording IR spectra all samples were prepared in KBr tablets. The spectra were recorded in the region of wavenumbers up to 4000 cm^{-1} by means of FT-IR spectrometer (Bruker IFS 66, Germany) in transmission mode (the number of scans corresponded to three) at room temperature. The accuracy of wave number determination was 0.2 cm^{-1}, and the accuracy of bandwidth determination was 0.1%. Recording and processing of all spectra was accomplished in OPUS 5.5 software.

Structural modeling of conium alkaloids in aqueous medium was carried out by means of Gaussian 09W employing Hartree-Fock theory. Solvation effects were taken into account within the framework of IEF-PCM model of reactive field [26,27]. In this model it is considered that the solute molecule is located in cavity, whose surface is represented as a set of spheres centered on the atoms of solute molecule with the radii determined by atomic van der Waals radii. An important feature of such model is the consideration of self-consistent influence of the cavity shape and electron density.

3. Results and discussions

Analysis of the possibility of formation of stable adducts between the alkaloid molecules and C_{60} fullerene was performed using numerical simulation and analysis of IR absorption spectra.

Fig. 1 demonstrates the results of calculation of IR spectrum of γ-coniceine as one of a conium component in vacuum and water. Considering the polarizing impact of aqueous environment the IR

absorption spectra of other conium alkaloids were also calculated (data not shown).

Assuming that (1) the contribution of individual alkaloids to experimental conium spectrum is additive, and (2) the contribution of the alkaloid molecules occupying the lowest energy state is dominant, the resulting IR spectrum of conium was calculated and compared with the experiment (Fig. 2).

The value of the Pearson rank correlation coefficient [28], computed for the curves in Fig. 2 (by means of uniform quantization in the range (3750–500) cm^{-1} with 700 points), was equal to 0.6 which is significantly higher than the critical value of the correlation coefficient equal to 0.261 for the significance level of 0.0005. It evidences relatively high similarity of the measured and computed spectra which confirms the appropriateness of the chosen computation method for determination of physical properties of the studied alkaloids.

Calculations of dipole moments and energies of the lowest state of the studied alkaloids (Table 1) have shown that the three molecules (γ-coniceine, conhydrine and pseudoconhydrine) in aqueous environment posses the most high values of dipole moments. It is known that this feature may cause formation of adducts which may be the case for these molecules when immersed to water.

In vacuum the values of dipole moments of all alkaloids are lower, which can be explained by the absence of induced polarization effect from aqueous environment. The highest value of dipole moment belongs to pseudoconhydrine. Such selective dependence of the dipole moment of conium alkaloids allows to manage their chemical activity on formation of adducts by changing the electric properties of environment.

Analysis of the data presented in Fig. 2 shows that the absorption band (3600–2800) cm^{-1} can be assigned to valent vibrations of N–H and C–H groups. The region (1800–400) cm^{-1} contains deformation vibrations of C–N, C–H and C–C groups, valent vibrations of C=C, C=N double bonds and C–C–C backbone vibrations. The 1684 cm^{-1} band (Fig. 1) present in the calculated spectrum of γ-coniceine is associated with the vibrations of γ-coniceine ring, in which the contribution of C=N double bond is dominant. In the spectra of two other alkaloids this band is absent (data not shown).

Of particular interest is the γ-coniceine molecule representing one of the conium alkaloids having a double bond connecting N and C atoms. This factor points out on the possibility of formation of
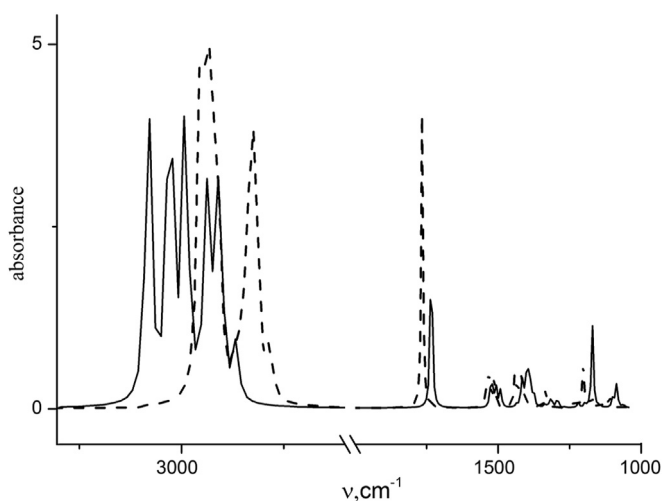

Fig. 1. Calculated IR absorption spectra of γ-coniceine in vacuum (solid line) and water (dashed line).
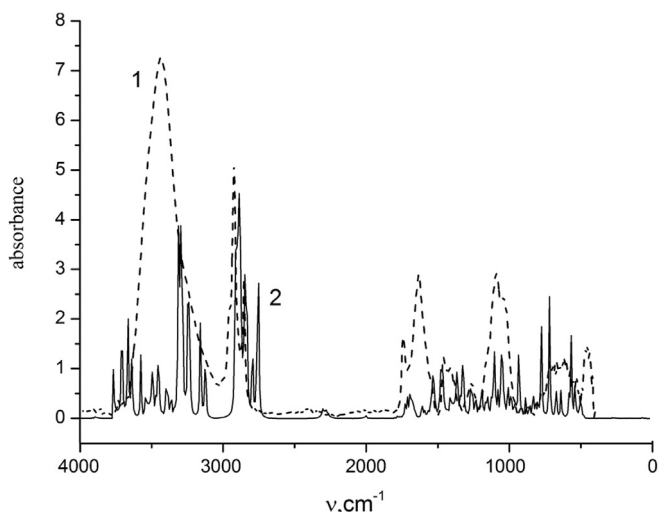

Fig. 2. Measured (1) and calculated (2) IR absorption spectra of conium in water.