"ALEXANDRU IOAN CUZA" UNIVERSITY OF IAŞI
FACULTY OF PHYSICS

SUMMARY OF THE PHD THESIS

CONTRIBUTIONS TO THE CHARACTERISATION OF INTERMOLECULAR INTERACTIONS IN SOLUTIONS OF ORGANIC COMPOUNDS

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The study of intermolecular interactions in solutions of organic compounds presents great interest due to the large amount of information that can be obtained: solvent effects, types of interactions, electro-optical parameters of the spectrally active molecules (dipole moment, polarisability, etc.). The characteristics of molecules can be studied by using various theoretical models and spectral techniques of investigation.

The study of intermolecular interactions presents a wide range of applications in various fields: medicine, chemistry, physics, etc.

The spectral methods used in the investigation of intermolecular interactions in solutions are highly useful, as they allow obtaining information on the internal structure of the liquid, the local fields of forces acting inside the liquids, reaction speed, equilibrium constants, etc.

In spectral research, active spectral molecules provide information on the intensity of intermolecular interactions by modifying their electronic spectra when passing from gas into liquid. In liquid theory [1,2,3], spectral modifications are correlated with electro-optical parameters of the solvents, so that at present it is possible both to describe the local order in liquid solutions, as well as the estimation of electro-optical parameters of the spectrally active molecule (dipole moment, polarisability).

In our PhD project, we studied the behaviour of some spectrally active molecules (pyridine, isoquinoline and 1,2,4-triazolium ylides and a series of azobenzene derivatives) in binary and ternary solutions, with a view to assess the nature and intensity of intermolecular interactions between them and the liquids they are solved in, as well as to estimate electro-optical parameters (dipolar moment, polarizability) in excited states, knowing their values in fundamental state. We studied the process of controlled release of 2 - [(1-benzyl-4-piperidyl) methyl]-5,6-dimethoxy-2,3dihidroinden-1-one (a drug used as palliative treatment in mild and moderate forms of Alzheimer's disease, as well as Glucose in hydroxypropyl-cellulose foils.

The thesis is structured into two parts: Part I: *Literature review* and Part II: *Personal contributions*, preceded by introduction and followed by *General conclusions*, *Bibliography* and

an *Annex* comprising the list of papers published in scientific journals and participations with oral presentations or posters at international and national conferences.

The first part of the thesis – the literature review – comprises two chapters. Chapter IA, *Intermolecular interactions in solutions* presents the classification and characterisation of intermolecular interactions in liquids, as well as the electro-optical parameters of some isolated molecules. Chapter IB, *Solvent influence on electronic absorption spectra* presents the theories on the influence of solvents on the electronic absorption spectra: McRae, Bakhshiev and Abe theories [2-4]. Furthermore, this chapter presents methods for the estimation of the contribution of various types of interaction (orientation-induction, polarisation-dispersion) to the total spectral shift of the electronic absorption spectra, as well as the spectral devices used in recording the electronic absorption spectra in the studied solutions. Chapter II, *Controlled release*, comprises the characterisation of the drugs controlled release phenomenon in various release systems, release mechanisms, especially that of diffusion and a few mathematical models describing the controlled release process [5].

Chapter III *Characterisation of the organic compounds studied in the thesis* is structured into two sub-chapters. The first sub-chapter is aimed at presenting the structure, stability and applications of the cycloimmonium ylides studied in the thesis: two pyridine and, respectively, two isoquinoline ylides, with applications in chemical and pharmaceutical industry, as precursors of the new heterocyclic compounds [6,7]. Another class of substances studied from the point of view of intermolecular interactions, consisted in the class of pyridazinium ylides, substances that proved to have an antifungal and antitumor action, some of them acting against the Koch bacillus [8]. In the thesis, we have equally studied some 1,2,4-triazolium ylides, substances that have a wide range of applications in the pharmaceutical industry, with a number of actions: antifungal, antimicrobial, antitumor, anticonvulsant, anti-HIV etc., as well as three derivatives of azobenzene [9]. The second subchapter describes and characterizes the electronic absorption bands of some cycloimmonium ylides studied in the thesis. Also, under the same sub-chapter are represented diagrams of the electronic levels involved in the emergence of electronic absorption bands for the analysis of the spectrally active molecules. The spectrally active molecules studied present an electronic absorption band with an intra-molecular charge transfer. The nature of this band is proven by the proportionality between the energy in the maximum of the visible absorption band of the studied cycloimmonium ylides and the empirical polarity Z of the solvent defined by

Kosower. The mechanism responsible for the apparition of this band is also demonstrated by the evolution of the intensity of the electronic absorption spectra in acid media. The electronic absorption bands with intramolecular charge transfer disappear in the acid environment due to the pair of carbanium electrons blocked by the free protons [10,11].

Chapter IV, entitled *Spectral study of some cycloimmonium ylides in binary and ternary solutions* comprises the results of the research conducted on the intermolecular interactions between the spectrally active molecules studied and the solvents in which they are dissolved. In the first two sub-chapters, empirical solvent ladders for binary and ternary solutions of some pyridazinium, pyridinium and isoquinolinium ylides were studied. The studies conducted indicated a similar sensitiveness of the solvents on the compounds with similar chemical structures. The third sub-chapter comprises the results obtained in the spectral study of some cycloimmonium ylides in binary solutions. Applying the existing solvent theories, orientation and specific interactions were separated in the binary solutions obtained with protic solvents [10,11]. The representation of the wavernumbers in the maximum of the electronic absorption band of the molecules studied in different solvents highlighted a separation of aprotic and protic solvents in the vicinity of distinct curves, the distance between them, can be an estimation of the contribution of the specific interaction in protic solvents. The solvatochromic analysis demonstrated that universal interactions prevail in aprotic solvents, while specific interactions also occur in protic solvents. The contribution of specific interactions was approximated by an additional term $k\delta_{OH}\,(ppm)$ which depends on the chemical shift $\delta_{OH}\,(ppm)$ measured in the NMR spectrum of the hydroxyl solvent. The separation of interactions in the binary solutions of cycloimmonium ylides studied indicated the significant contribution of specific interactions to spectral shifts, interactions neglected in the existent theories. Thus, for the binary solutions of pyridinium and iso-quinoinium di-carbetoxi metylide, the input of specific interactions to the total spectral shift is of approximately 50% for all the studied solutions [12]. Solvatochromic studies in binary solutions of the studied ylides permitted the calculation of the dipole moment in their excited state, using the data provided by the HypperChem program for the corresponding measures in fundamental state, as well as the molecules dimensions (molecular radius, surface, volume). The dipole moment of the studied pyridinium and isoquinolinium ylides decreases by excitation [10,11].

In a section of this sub-chapter are given the results obtained from the spectral studies conducted on binary solutions of three compounds of azobenzene ADi(i=1-3). The spectral data was correlated with the data obtained from quanto-mechanical modelling with the help of the HyperChem program. Correlating the results obtained by these two research methods, we obtained information regarding the dipole moment and the polarizabilities of the compound studied in excited state. The dipole moments in excited state of the azo-benzene derivatives studied have greater values compared to those corresponding to the fundamental state. The electric polarisability of the azo-benzene derivatives increases by excitation. Solvatochromic studies of azo-benzene derivatives allowed for the determination of the input of each type of interaction to the total spectral shift. The input of specific interactions in the binary solutions of the azo-benzene derivatives studied was determined by means of the Kamlet-Taft solvent parameters: β expressing the capacity of the solvent to donate protons to the creation of the hydrogen bond; α, the capacity of the solvent to accept protons to the creation of the hydrogen bond. For the binary solutions obtained by means of n-Hexane, we highlighted universal, orientation and dispersion-induction interactions, the input of dispersion-induction interactions prevailing (87% for the AD1 compound and 96% for AD2, respectively AD3). In the binary solutions of these compounds, obtained with methanol, we separated universal, orientation (36% for AD1, 14% for AD2 and 15% for AD3), induction-dispersion (53% for AD1, 68% for AD2 and 72% for AD3), but also specific interactions conducted through the transfer of protons from ADi(i=1-3) compounds to the molecules of the solvent (8% for AD1, respectively AD2 and 9% for AD3), as well as interactions specifically carried out through the transfer of protons from the molecules of the solvent to derivatives of azo-benzene (3% for AD1, 10% for AD2 and 4% for AD3) [13].

The study of ternary solutions provided information on the specific interaction of N-ylides in protic solvents, the composition of the first solvating sphere, the polarisability of molecules in excited state, as well as the estimation of the difference between the interaction energies between the pairs of molecules ylide-active solvent and ylide-inactive solvent. The research carried out indicated the non-homogeneity of the ternary solutions of the studied ylides, highlighted by the non-void values of the excess function δ_1 and the values differing from the unit of the preferential solution constant k_{12}. For the ternary solutions Octanol(1) + Dicloretan(2) + ylides, the first solvation layer of the ylide contains a higher number of active solvent molecules (Octanol) in

comparison with the rest of the binary solvent [11]. The study of the composition of the first solvation layer of triazolium ylides in ternary solutions with Methanol (1) and Benzene (2) indicated the preferential presence of Methanol in the first solvation layer, compared to the rest of the solution. The non-homogeneity of the ternary solution is more pronounced for equimolar fractions of the two solvents [14]. The statistical model of the solutions with three components [15] allowed for the assessment of the differences between the potential interaction energies in pairs of the type N-ylide-protic solvent and N-ylide-aprotic solvent. This difference is proportional to the strength of the hydrogen bond that is established between the N-ylide and the protic solvent. For the protic binary solvents, the difference between the interaction energies in pairs comprises the difference between the energies corresponding to the formation of hydrogen bonds between the two types of complexes between the spectrally active molecules and the two types of protic solvents. The order of magnitude of these differences corresponds to the weak hydrogen bonds [16].

Chapter V, *Spectral control of the control release process of some compounds in polymer foils* is structured into two sub-chapters and it comprises the results of the research carried out with the help of several methods (measurements of the contact angle, AFM technique, spectral methods) on the polyvinyl alcohol polymeric foils in which Donepezil was incorporated in various concentrations, as well as on the hydroxypropyl-cellulose in which glucose was introduced in different proportions. We investigated the influence of the stretching process on Donepezil release in PVA, elucidating the mechanisms involved in the dynamics of the drug release kinetics in the human body, depending on the stretching degree. To this purpose, 2% Donepezil PVA foils were obtained and characterised using measures of the contact angle, the AFM technique and optical methods. The 2% Donepezil polymer foils have a lower water contact angle compared to pure PVA foils. The contact angle with ethanol is higher for the foils containing the drug. The morphology of the foils surface is modified both by the presence of Donepezil and by the stretching process. Rapid release was noticed during the first 60 minutes of immersion. Non-stretched foils had slower release, compared to extended foils. The total quantity of Donepezil released increased with the degree of stretching. These results testify to the dependence of drug release kinetics on its arrangement in the polymer matrix. Additionally, based on the Korsmeyer Peppas model, diffusion coefficients were estimated and the following conclusions were issued:

the diffusion coefficient *n* increases linearly with the stretching degree; *n* keeps its values in the field corresponding to the abnormal delivery of the drug in the polymer matrix [17].

The study on the release of glucose in polymer foils of hydroxypropyl-cellulose highlighted the important role of the polymer content in the release systems on drug release kinetics. We prepared and investigated, from a morphological point of view, release systems having hydroxypropyl-cellulose as polymeric matrix in which glucose was included in various concentrations. The physio-chemical properties of the release system components and the polymer-drug ratio govern the release of the drug from the system. The *in-vitro* release data analysis, supplemented by various kinetic models, has shown that for a small percentage of glucose in the sample, the release process is best described by Fick's diffusion. In the samples with higher glucose content, abnormal diffusion was highlighted, determined by polymer matrix hydration and swelling, drug diffusion and, finally, erosion and degradation of the matrix.

The analysis of the data obtained for all the studied samples led to the identification of the best drug release formula (2 ml solution of glucose with the concentration of 1,8 mg/ml mixed with 4 ml HPC solution of 20% concentration), which can guarantee a constant drug dose for a longer time.

At the end of the thesis, the General conclusions point to the original contribution brought to the study of intermolecular interactions and the process of controlled drug release in polymer foils (polyvinyl alcohol and hydroxypropyl cellulose). The results of the research conducted throughout the doctoral studies were published in journals indexed in ISI Thmoson Reuters and BDI. Seven papers were published in ISI journals and three were sent for publication. Moreover, two papers were published in BDI journals. During the doctoral studies, the results of our research were presented on the occasion of several national and international conferences (five oral presentations and seven posters presented in International Conferences).

Keywords:

Intermolecular interactions, binary solutions, ternary solutions, electronic absorption spectra, pyridinium ylides, iso-quinolinium ylides, pyridazinium ylides, azo-benzene derivatives, 1,2, 4 - triazolium-ylides, polyvynil alcohol, hydroxypropyl-cellulose, donepezil, glucose, interactions split, statistical model of ternary solutions, potential energy in pairs of molecules, controlled release.

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