Laboratory of Physical and Chemical Research Methods

Laboratory of Physical-Chemical Methods of Study

Laboratory head

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In 1976, young bright-minded scientist, Takhir Fatikhovich Aripov (an Academician in the years to come) took the lead of the Optical-Analytic group (subsequently Laboratory of Physical-Chemical Methods of Study) at the Bioorganic Chemistry Department under Uzbekistan Academy of Sciences. At that time, the Bioorganic Chemistry Department dealt with protein toxic components of the venoms from the snakes and the arthropods with neurotoxic and cytotoxic effects. The spacious research mind and deep research intuition, as well as continuous communications and personal contacts with the leading scientists in the membranology enabled him to solve the structural problems of lipid-protein interactions in a short time. As the result of this person's activity, the laboratory was equipped with the devices of differential scanning calorimetry, with a small-angle neutron scattering (SANS) diffractometer and experimental model of a spectrometer to measure the phosphorescence in biological systems. The 200 mHz nuclear magnetic resonance spectrometer (Varian, USA) was put into operation; biochemical methods for isolation and characterization of cytotoxic components of Naja naja oxiana cobra, namely, of cytotoxins and phospholipases, were set up. Within that period of time, Professor Aripov put in great efforts for all young workers of the laboratory to undertake an internship at the stitute of Crystallography and Institute of Chemical Physics, USSR Academy of Sciences, and All-Union Cardiological Research Center, USSR Public Healthcare Ministry.

As time went by, the priorities of research directions associated with objective reality changed. It was necessary to change or propose novel approaches to the studies meeting the demands of current life. Among other things, the priorities included production of novel medications from the local raw materials. Traditionally, the Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, dealt with efficient medications for wide spectrum of diseases. These include various anti-viral and anti-chlamydial drugs based on gossypol and its derivatives, interferon inducing medications to control external pathogens, as well as various hemostatic and antioxidant medications.

Transport of Ca^{2+} ions through plasma membranes being of special interest due to extreme multiplicity of mechanisms and ways to produce effects of the process on the cell functions and the whole metabolism is another direction of research at the laboratory.

For many years, unique properties of gossypol have been comprehensively studied. It served as a basis for multiple derivatives, to name, megosin, rometin and others, possessing low toxicity and higher biological efficacy. We demonstrated that the compounds in a dose-dependent manner increase concentrations of cytosol calcium; the effect is achieved due to activation of outward intake, depletion of intracellular pools, and increase in calcium membrane permeability, inhibition of calmodulin-dependent processes and effect of arachidonic acid on the metabolism.

X-ray structural analysis of low molecular weight active compounds is among the significant research directions of the laboratory, supported by Takhir Fatikhovich from the very onset. By the time of the laboratory foundation, some young workers, including B.T. Ibragimov, future Academician, and S.A.

Talipov, future head of the laboratory, have been thoroughly schooled at the laboratory of Prof. Tischenko G.N. at the Institute of Crystallography, USSR Academy of Sciences. The alkaloids isolated from various Uzbekistan endemic plants, and mainly gossypol, a unique polyphenol compound isolated from the cotton roots, were the main objects of study at that time. As the X-ray structural analysis was the principal one in the study on the structures of crystalline low molecular weight compounds at the laboratory, the acquirement of four-circle automatic diffractometer SYTEX P21 in the middle 1970s might denote that the structural studies were propelled to the next level.

For many decades, many researchers registered the variability in some physical-chemical parameters, such as melting point and solubility of gossypol. However, for quite a long time the nature of the phenomenon defied explanation. Forty years of studies under way at the Laboratory of Physical-Chemical Methods of Study demonstrated that the variability in question is caused by its unique capability to the formation of clathrates. Gossypol was established to be able to form compounds of inclusion practically with all low molecular weight compounds (they are nearly 100).

At the Laboratory of Physical-Chemical Methods of Study, many-year enormous experimental material has been accumulated in studying dependence of formation for polymorphic and clathrate structures on conditions of crystallization. The structures of all crystal modifications of clathrates obtained at various temperatures (higher and lower than the room one) were determined by the X-ray structural analysis. The structures of modifications were analyzed by temperatures of formation for clean-cut correlation between the structure and temperature of crystallization to be found. The dependence in question was formulated as the following law.

In the supramolecular chemistry, crystal inclusion compounds hold a specific place. The molecules of one compound (guest) occupy the cavities between relatively large molecules of another compound (host). That is why they are called host-guest complexes or clathrates (solvates), the clathrate-forming compound is clathratogen. Each third organic compound is a clathratogen. There are multiple universal clathratogens forming the host-guest complexes with many guests, but there is no a clathratogen forming clathrates with all relatively small compounds (an absolute clathratogen).

The researchers from the Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, headed by Professor B.T. Ibragimov demonstrated the presence of the clathratogen like this on gossypol, biologically active pigment of the cotton. The evidence for presence of modifications of one and the same clathrate (polymorphs) in the case of universal clathratogens is the essence of the second discovery. These two discoveries facilitated the third one, that is, the establishment of new law of nature governing the determination of dependence of structures of polymorphs of the clathrate on the temperature of its formation.

The discoveries won international acclaim. All basic papers were written in English and published abroad in the high class journals. There were 102 works published, 2 books and 52 journal papers among them. The findings were reported and discussed at 35 international scientific forums taken place in 17 countries. Foreign scientists checked the discoveries up in their studies to confirm their validity. They make their references to the discoveries and use them in their studies. At their suggestion, the new law was called after Uzbek scientist who discovered it as “Ibragimov’s rule”.

Discoveries of our scientists are of great scientific-practical value for supramolecular and physical chemistry, material science and pharmaceutics. “Ibragimov’s rule” made possible solving a number of urgent and significant applied tasks. Thus, now researchers can control structures of clathrates for various practical purposes, to produce medications, contaminated by a solvent in their solvates, in the pure form by simple recrystallization at the temperature close to boiling point of the solvent. For the first time the law in question was published in 1999 in “Inclusion Phenomena and Macrocyclic Chemistry”. Its basics were reported at the plenary meetings of conferences in Novosibirsk, Notr-Dam (USA), Liege (Belgium) and in Istanbul to get the name of “Ibragimov’s rule”. Its modified variant was published in 2007 “Crystal

Engineering Communications" as an opening review article.

The establishment of the law stimulated efforts in the international research of polymorphism of clathrates based on the universal clathratogens. The works conducted in the area in Australia, South Africa Republic, Germany and USA activated. The international seminar of 2003 in Novosibirsk the rule was proposed to be called after the scientist who established the rule, that is, "Ibragimov's rule".

The responses of foreign scientists demonstrated at multiple international conferences and symposiums on inclusion compounds are the evidence for recognition of the law at the international level.

Traditionally, the laboratory uses a wide complex of physical-chemical methods, to name, nuclear magnetic resonance and electron paramagnetic resonance, methods of optic spectroscopy, such as infrared and ultraviolet, fluorescent spectroscopy, X-ray structural analysis, differential scanning calorimetry, measurement of conductivity of planar bilayer lipid membranes and other biophysical methods. Study on the structure of biologically active compounds, organic complexes, mixed ligand-metal complexes as well as of interactions of physiologically active compounds with the components of a cell by physical-chemical methods is the principle research directions at the laboratory. Development of production technologies and study on biological activity of biologically active supplements based on the local raw materials is a novel direction.

Research directions include

- Study on crystal inclusion compounds or host-guest complexes (clathrates) by X-ray structural analysis. The clathrates of gossypol and its derivatives, inclusion compounds of physiologically active compounds with native and modified cyclodextrines, molecular and metal complexes based on monosubstituted (nitro-, amino- and hydroxy-) derivatives of benzoic acid with ethanolamines
- Study on conditions for formation of coordination compounds, particularly, of mixed ligand bioactive metal complexes, as well as on interrelations of the structure and biological activity
- Study on anti-radical and antioxidant activity of physiologically active compounds of plant and animal origins to provide necessary biopharamaceutical requirements in production of various medications and biologically active supplements

Principle results include

- Synthesis of metal complexes based on low molecular weight heterocyclic carboxyl-containing bioactive compounds (as ligands) with transition metals as well as mixed complexes with di- and triethanolamines and ethylendiamine. The additive property of the components of supramolecular complexes, conditions for formation, their stability, peculiarities, features of crystal structure, possibility to generate polymorphic forms and thermodynamic resistance
- Establishment of growth-stimulating and fungicide activity of basal compounds and their complexes *in vitro*
- Determination of effects of the complexes on the activity of peroxidase in the anti-oxidant system of the cotton
- Proposition of the antihypoxant activity of new polyphenol compounds from Euphorbia family proved by preclinical studies on mice lines in vivo, based on the model of functional parameters of mitochondria,

- Achievement of the increase in the solubility and bioaccessibility of cynaroside, a flavon, based on native and modified cyclodextrines. TG–DSC and powder diffractometry demonstrated formation of new phases upon generation of complexes of cynaroside with cyclodextrins by methods of co-evaporation and co-grounding
- Development of two biologically active supplements in the form of syrups: «Tinchitish-Shifo" to be recommended for relief of the anxiety associated with the unfavorable weather, external irritating factors and blood pressure rise, and «Buyurak-Shifo» to be recommended in kidney and urinary tract diseases

Practical value of the results

- Generation of additive effect of supramolecular complexes as compared with those produced by their components
- Generation of plant growth stimulators and compounds with fungicidal properties acting in micro-concentrations by synthesis of mixed ligand complex compounds of biometals with carbonic acids and amino alcohols
- Development of novel biologically active supplements based on the local raw materials with optimal ratio of components
- Biopharmaceutical optimization of biologically active compounds by placing them into the cyclodextrin matrix
- Effective solid phase synthesis of non-symmetric monoamine derivatives of gossypol on the gossypol-zeolite matrix

Research results

- The structures of 70 novel compounds were determined by PCA to enter the Cambridge Crystallographic Data Center in Great Britain (The Cambridge Structural Database, https://www.ccdc.cam. ac.uk/solutions/csd-system/components/csd/). The compounds are used in the synthesis and description of structures of similar compounds
- Two patent applications were filed: No. IAP 05679 "Heteroligand complex of Cu(II) with monoethanolamine and 2.4-dichlotophenoxyacetic acid" 30.10.2018 and No. IAP 05680 "Heteroligand complex of ZN(II) with monoethylamine and 2.4-dichlotophenoxyacetic acid" 30.10.2018
- In the frames of State Scientific and Engineering Program, the documentation packet was planned to be prepared for registration with Uzbekistan Public Healthcare Ministry and production of biologically active supplements in the "Bioton" Company Ltd.

Services

- The X-ray structural studies on monocrystal and polycrystal organic and non-organic compounds by means of the CCD Xcalibur Ruby (AgilentTechnologies, USA) и XRD-6100 (Shimadzu, Japan)

diffractometers

- Thermoanalytical studies by means of TG-DSC analyzer NETZSCH STA-409 PG (Germany)
- Chromatographic-mass spectrometric studies by means of the Agilent 6420 (USA)
- Determination of anti-radical and antioxidant activity of biologically active compounds, qualitative and quantitative compositions of the plant extracts

Scientific ties

Slovak Agricultural University (Nitra, Slovakia), Autonomic University of Barcelona (Spain), Technical University of Freiburg (Germany), University of Bern (Switzerland), University of Ohio state (USA), Claude Bernard University (France), Nottingham University (Great Britain), Adam Mickiewicz University (Poland), RWTH Aachen University (Germany), Central Asian Center for Development of Medications, Chinese Academy of Sciences (China)

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