

## Professor Bogdan Jordanov Kurtev, Member of BAS - Builder of Modern Organic Chemistry in Bulgaria



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The career of Professor Bogdan J. Kurtev as a leading chemist in Bulgaria began in 1958 when at the age of 41 he was appointed to the responsible post of Director of the Chemical Institute at the Bulgarian Academy of Sciences (BAS). In 1960 this institute was split into two: Institute of General and Inorganic Chemistry and Institute of Organic Chemistry (IOC). B. Kurtev became the first Director of the latter and remained on this post till 1989. Upon his appointment B. Kurtev had the experience of seven years teaching organic chemistry as Docent at the Chair of Organic Chemistry, Vice Dean of the Physical Mathematical Faculty and a Ph.D. degree (1950) obtained in the prestigious Moscow Chemical Technological Institute “D. I. Mendeleev” under Acad. V. M. Rodionov on the synthesis of  $\beta$ -naphthyl- $\beta$ -amino acids by means of the Rodionov reaction and uracils derived from the amino acids.



Prof. Vladimir Rodionov with collaborators.

His scientific capacity is illustrated by his appointment as assistant in organic chemistry by Professor D. Ivanov in Nov 1940 immediately following his graduation taking into account the limited number of positions at the time.

In the first postwar decades several challenges faced Bulgarian Chemistry. The sheer increase of number of students trained was dramatic. Before the war Sofia University the single provider of chemical education had an input per annum of *ca.* 20 students, in 1953 the number increased to 120, larger numbers were taught in the new Higher Institute of Chemical Technology and many other institutions. The scope of research fields rapidly increased with the demands of fast growing industry in socialist Bulgaria.

Organic chemistry itself underwent a great transformation. The perception of organic chemists as skillful experimenters of exceptional memory changed with the development of theoretical methods of explaining and predicting chemical behavior of organic compounds. No less was the importance of the new “physical” or “instrumental” methods. The handicap of Stalin’s purging science of “idealistic” theories in the early 1950’s, such as Linus Pauling’s resonance theory, took more than a decade to shake off in organic chemistry education. Feeling the importance of modern interpretation of organic chemistry, in 1957 B. Kurtev developed and taught the advanced course “Structure and Reactivity of Organic Compounds” - first of its kind in Bulgaria. It encompassed stereochemistry, conformational analysis, mechanisms of organic reactions, quantitative correlations of reactivity (the basis of QSAR in more recent times).

B. Kurtev proved exceptionally suitable to meet these challenges as person of very high intelligence, well versed in most fields of chemistry besides organic, of sound administrative skills. As Director of IOC he interviewed each appointee; an important characteristic for him was the dedication towards research which he tested by inquiring about their Master’s Thesis even the m.p. of compounds obtained. His integrity and sense of justice were beyond dispute. The following example was typical - in 1962 in Prague the IUPAC Conference on Natural Products was attended by elite of organic chemistry. The lab of organic synthesis suggested

the participation of B. Kurtev, J. Stefanovsky and I. Pojarlieff. The central management of BAS approved a grant for the Director; the two young scientists were permitted to attend on their own expenses. B. Kurtev said this was unfair and shared his grant in three equal parts. Witness of the enthusiasm of our lab remain the autographs of Nobel Prize winners Ruzicka, Prelog, Woodward, Robinson, Todd, Barton written on the book *Perspectives in Organic Chemistry* edited by Sir Alexander Todd. More importantly he used contacts with distinguished scientists from the other side of the iron curtain to obtain grants for talented young researchers interested in a particular field. Personal applications/invitations were forbidden by default. B. Kurtev would ask for a nameless invitation to IOC and had the authority to make the Party bureau nominate the prearranged person. Upon rare occasions the Party changed the nomination which, however, destroyed the deal. B. Kurtev could be successful in his policies even at the expense of by-passing rules because of his authority and trust by the Party. I believe loyalty to socialism was predetermined by the fact that his father Jordan Kurtev was executed without trial in September 1923 as a communist. This happened during the uprising against the fascist coup d'état, shot and thrown from the rocks over river Iskar at the railway station Lakatnik. The father, Jordan Kurtev, worked in the analytical laboratory of the copper mines in nearby Eliseina. He had a degree in chemistry from Sofia University and further education in Germany and Toronto, Canada.

Characteristically B. Kurtev and his coworkers were open to the world, joint research was carried out with labs in Hungary, France, Germany, England, Latvia, Lithuania to mention some.

B. Kurtev was instrumental in much of the rapid development of the chemical sciences in BAS as Head of the Department of Chemical Sciences of BAS since 1962 while holding his Directorship of IOC simultaneously. The Department evolved into Unified Center of Chemical Sciences in BAS (1973), unified referring to closer links with the Chemical Faculty of Sofia University. B. Kurtev served also as Vice-president of BAS 1971-73. One of the biggest achievements was the generous UNESCO grant for creating a Centre of Phytochemistry (CP) based on the existing powerful labs researching ethereal oils, alkaloids, lipids, proteins, enzymes. This provided the IOCCP with a new building and modern infrastructure e.g. the first mass spectrometer in Bulgaria.

Before and after the war organic chemistry research in Sofia was dominated by the outstanding figure of Professor D. Ivanov elaborating on the "officially named" Ivanov reaction, the theme of the Ph.D. theses of many future professors. Professor B. Kurtev never published a paper with D. Ivanov; after being appointed as assistant at the end of 1940 he was soon conscripted first in the cavalry regiment at Breznik and then in an antiaircraft artillery unit in Dedeagach (now Alexandroupouli) on the Aegean. After the war he was transferred as assistant to the Chair of Medical Chemistry at the Higher Institute of Medicine under Professor Alexander Spassow with whom in 1946 he published in German his first two papers on the preparation of 3-pyrazolidones from phenylhydrazides of  $\beta$ -hydroxy acids.

Most broadly the scientific contributions of Professor Kurtev can be grouped in the following fields:

*A. Mechanisms, stereochemistry, and synthetic applications of aldol type reactions where-by a C-C bond is formed by base or acid catalysed addition of a C-H to a carbonyl or imine double bond*

The following list is in roughly chronological order. The names in parenthesis are the main coworkers. In many cases the products contain a 1,2-diphenylethane skeleton disubstituted in the 1 and 2 positions.

Reaction of Schiff bases and hydramides with esters of phenylacetic acids catalyzed by anhydrous  $AlCl_3$  (N. Mollov). Kurtev and Mollov first used this catalyst for such condensations creating a convenient method of preparing the *erythro* esters in good yields. The stereoselectivity was shown to be due to equilibration of the diastereomers and lower solubility of the preferred isomer.

Base catalysis by alkaline alcoholates, amides and hydrides of the above reaction including the dimethylamides of phenylacetic acid (E. Simova, J. Stefanovski) has afforded high yields and *erythro/threo* selectivities in cases ranging from 10:1 to 1:10.

The Rodionov reaction (I. Pojarlieff) provides  $\beta$ -amino acids by heating an aromatic aldehyde (aliphatic give lower yields) with malonic acid in an ethanol solution of ammonia. The new pair acetaldehyde and methylmalonic acid was chosen to obtain a 1,2-dimethyl analogues to the 1,2-diphenyl system. Low yields and low selectivity prompted a stereospecific synthesis from the isomeric 2,3-dimethylsuccinic acid *via* the

Hoffmann rearrangement of the monoamides – yielding relative configurations and high yields of the pure isomers.

The Perkin Reaction (C. Krachanov) yields cinnamic acid upon heating an aromatic aldehyde in acetic anhydride in the presence of base. The reaction goes through the aldol intermediate - the respective  $\beta$ -hydroxy anhydride. Kinetic results of Kurtev and Krachanov for the elimination stage of the *erythro/threo* isomers of the product from benzaldehyde and phenylacetic acid indicated larger activation energy (larger temperature coefficient) for the elimination stage, *i.e.* at low temperatures the elimination would be arrested which led to the discovery of a new method of preparing  $\beta$ -hydroxy- $\alpha,\beta$ -diphenylpropionic acids. It showed *erythro* selectivity opposite to the Ivanov reaction.



With Prof. Christo Kratchanov.

Significant contributions to the mechanism and synthetic applications were also made to important organic reaction: Reformatski (M. Mladenova, B. Blagoev), Ivanov reagents and reaction (M. Mladenova, B. Blagoev), Low temperature Claisen Condensation (C. Kratchanov, N. Kirtchev), Erlenmeyer-Plöchl (I. Kavrakova, E. Simova).

### B. Cyclization reactions

The above reactions yielded as products open-chain diastereomer derivatives which could be readily converted into heterocycles of interest *per se* ( $\beta$ -lactams, dihydouracils, tetrahydro-1,3-oxazines, and 1,3-oxazin-2-ones, to name a few). Such cyclizations were also studied to assign the relative configurations (*erythro/threo*). In cases of stereospecific ring closure the *cis-trans* isomerism of heterocycles obtained present direct proof of the configuration of initial open-chain diastereomers.

In many cases the configuration had to be deduced from the rate of ring-closure presuming different stabilities of transition or ground states. The formation of  $\beta$ -lactams from  $\beta$ -phenylamino- $\alpha,\beta$ -diphenylpropionic acids (N. Mollov, E. Simova, J. Stefanovski), N $\rightarrow$ O benzoyl migration in 3-aminopropanols (N. Mollov, A. Orahovats), dihydouracils (M. Lyapova, I. Pojarlieff), present such examples.



A part of Lab. Mechanism of Organic and Enzyme Reactions and Organic Synthesis, 1980. The first row from left to right: Prof. Blagoy Blagoev, Prof. Nina Berova, Prof. Bogdan Kurtev, Assoc. Prof. Iva Blagoeva, Prof. Jury Stefanovsky.

This research stimulated the interest of Professor Kurtev into the factors governing reactivity in cyclization reactions. As early as 1959 with Mollov and Simova he applied the concept of favoured conformations along the lines of what became known as the Winstein-Holness equation to assign configurations of  $\beta$ -aniline- $\alpha,\beta$ -diphenylpropionic acids. The reactivities were quantified by measuring kinetics of cyclization and their activation parameters (I. Pojarlieff, I. Blagoeva, A. Orahovats, V. Fodor).

Expanding the substituent pattern in the open chain compounds allowed important contributions to be made in understanding the *gem*-dimethyleffect (I. Pojarlieff, I. Blagoeva). This steric effect is readily understood in small ring formation, but puzzling in six or five membered rings because hindrance by substituents instead of decreasing increases the rates of cyclizations. The driving force is actually the fact that *syn* interactions between the substituents in the open chain actually decrease in the ring since they become interactions of the members of the ring itself, *e.g.* the *syn* interaction of two methyl groups of 0.8 kcal/mol compared to the *anti* form is



relieved if butane is incorporated in the cycle chain. That enthalpy is the driving force of the effect was confirmed by successful correlations of seven reaction series of the *gem* effect with steric strain energies and following more precise molecular mechanics studies of P. Ivanov.

Stereoelectronic effect in N→O and O→N acyl migrations (M. Lyapova, I. Pojarlieff) were nicely demonstrated by means of the 1,2,3-triphenylpropane system developed by Kurtev and Lyapova where *N*-methylation in 1,3-aminopropanols inversed reactivities of the stereoisomers. The examples were included in Deslongchamps's book on stereoelectronic effects. These effects were later shown to apply in the case of 1,3-aminopropan-thiols by V. Kurteva, M. Lyapova, I. Pojarlieff.



With Assoc. Prof. Maria Lyapova and Prof. Jury Stefanovsky.

### C. Stereochemistry

Characteristically B. Kurtev demanded precision in experiment and interpretation. To this end the configuration of a wide range of derivatives was ultimately proven by chemical transformations. Thus the *erythro/threo* assignments of the  $\beta$ -amino- $\alpha,\beta$ -diphenylpropionic acids were unequivocally established by stereospecific conversion into *meso* and racemic stilbenediamines (J. Stefanovsky). The link between the amino and phenylamino series was established by phenylation of the amino group in a stereospecific reaction (N. Berova, E. Simova).

The resolution of the 1-menthyl esters of  $\beta$ -amino- $\alpha,\beta$ -diphenylpropionic acids into the four optically active isomers opened a new line of research (N. Berova, J. Stefanovski). The chiral aminopropanols obtained upon reduction proved useful substrates for structure/optical rotation relationships based on the contributions of chiral segments in the various conformations. The

unexpected result transpired that preferred in the *threo* diastereomers were conformations with *syn* phenyl groups which ran against Cram's rule that the two large substituents, *i.e.* the phenyl groups will prefer the *anti* conformation. In 1966  $^1\text{H}$  NMR (G. Fodor, R. E. Reavill, J. Stefanovsky, H. J. Bernstein) obtained large  $J_{23}$  for both epimers reliably showing preferred *syn* phenyls in the *threo* isomer. Later this was found to be quite universal *e.g.* work of S. Spassov and gave rise to a host of studies to explain this phenomenon. The extensive and elaborate computational studies of P. Ivanov answered most of the problems.

A versatile branch of the studies of optical activity was the work on Circular Dichroism and Absolute Configuration of key compounds with phenylsubstituents (N. Berova, P. Ivanov, G. Snatzke).



With Prof. Nina Berova



Prof. Gunter Snatzke and Prof. Carl Djerassi in front of IOCCP, Sofia.

The chromatographic behaviour of diastereomers (M. Palamareva, L. Snyder) of great importance for practical purposes was extensively studied from the view point of chromatographic theory and structure of substrates creating rules and computer programs for successful separation of open chain and cyclic compounds.

The geometry and conformations of many heterocyclic systems have been examined by means of NMR (S. Spassov, I. Pojarlieff, A. R. Katritzky). A study of the biologically important dihydrouacil, including dihydroorotic acid, has been widely cited.



With Prof. Katritzky and collaborators; Norwich 1965.

The existence of allylic strain in six-membered heterocycles with an endocyclic *N*-substituted amide group and a neighbouring substituent (I. Pojarlieff, M. Lyapova, A. Orahovats) could explain the significant effects of *N*-substitution on conformational equilibria in tetrahydro-1,3-oxazin-2-ones, hexahydropyrimidine-2-ones and hexahydropyrimidine-2,4-diones. A contribution to atropisomerism (S. Simova, Z. Beresnevičiu) was the assignment of the solution conformations of the atropisomers of some 1-(1-naphthyl)-hexahydro-2,4-dioxo(or 2-thio-4-oxo)-pyrimidines.

#### *D. Applied research*

B. Kurtev took active interest and was involved in practically almost all such projects in IOC (with a Centre of Phytochemistry) as well as many projects of the Unified Centre of Chemical Sciences. I will illustrate his activity with one of largest industrial projects of BAS in the 1970's "Bright Acid Copper Plating Agent B-7211" – carried out by a joint team from IOC and IPC (Institute of Physical Chemistry) (I. Juchnovski, I. Pojarlieff, S. Rashkov). For five years the whole

road was undergone from research, developing and implementing the manufacturing of the additive in the dye factory in Kostenetz, Bulgaria. B-7211 was used for the production of ca. 1 500 000 cars annually (Lada, Moskvich, Škoda, Wartburg, Volga, Zaporozhetz) between 1975-1990.



From left to right: Prof. Ivan Juhnovsky, Prof. Ivan Pojarlieff, Prof. Stefan Rashkov.

Our consultations with B. Kurtev were almost weekly and involved both administrative matters and scientific problems. Contrary to the common practice of leading managers to participate as authors of patents only on the merit of their administrative position motivated by financial awards, Professors B. Kurtev and R. Kaishev (Director of IPC) refused to participate as authors. They were forced to break their rules for parity reasons with the Directors from the Lithuanian AS and Soviet Industry Directors in just three patents concerning subsequent versions (BS-1 and BS-2) of the additive B-7211 developed by a joint Bulgarian-Soviet team.

#### CONCLUSION

The above non exhaustive overview of the work of B. Kurtev, I believe, suffices to name him as a builder of modern organic chemistry in Bulgaria bringing the inheritance of D. Ivanov, A. Zlatarov, and P. Raykov to a higher, more advanced level in the second half of the 20<sup>th</sup> century.

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