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OCTOGENARIAN RETROSPECTIVE

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This is a review concerning the main results obtained by the author in physical chemistry and applications to molecular biology. The domains considered are applied quantum chemistry; QSAR – minimal steric (topologic) difference; specificity of biologic processes; mathematical models for gene and cell cycle regulation. Some pertinent information concerning the research work of the main coworkers, especially of I. Bădilescu, is also given. The author published about 350 scientific papers in the above mentioned domains, and a calculated h=15 Hirsch factor, as scientometric results.

INTRODUCTION. SHORT C.V.

I was born in Timişoara, in 1935, in a typical middle class family. My interest for chemistry started in the high school. I studied chemistry at the University of Bucharest from 1952 to 1957. The doctor title in physical chemistry under the guidance of professor I. G. Murgulescu was obtained in 1965. Interests in molecular biology were added starting with 1962. In 1965 I returned to the home town as professor for physical chemistry at the University of Timişoara. During the period 1977-1997 I taught biophysics at the University of Medicine and I finished my active career around 2010 at the Institute of Chemistry Timişoara of the Romanian Academy. In 1997 I was elected as corresponding member of the Roumanian Academy.

This retrospective starts with description of publications in applied quantum chemistry. A description of work in the field of quantitative structure – activity relationships (QSAR) follows. Then, mathematical cell regulation models and contributions to the theory of specificity in biological processes are described.

Most of the research described here was performed in cooperation with friends and colleagues. Their names appear in the references and some details concerning their research in a final paragraph.

RESULTS IN APPLIED QUANTUM CHEMISTRY

After graduating in 1957, my main research line was the theory of unimolecular reactions, especially activation energy (E_a) predictions, under the guidance of professor I. G. Murgulescu and dr. Tatiana Oncescu. My main research tool was the HMO (Hückel Molecular Orbital) method, as described in the, then modern, treatises of Streitwieser or Coulson.[1] In addition to this, a second research line, applications to spectra and reactivity of organic molecules, started a lifelong collaboration with A. T. Balaban.

Activation energy (E_a) calculations for cis-trans isomerisations of a,β- disubstituted ethylene derivatives in gaseous phase was my first important success.[2] In the activated complex, for 90^o torsion around the ethylenic double bond, the pi (π) – electronic conjugation should be interrupted. Then E_a should be equal to the difference of delocalization energies (ΔDE), as calculated by the HMO – method. The

calculated activation energies (ΔDE) and experimental E_a values are listed in Table 1. The β=32.5 kcal/mol value was calibrated equating ΔDE=2β for dideutheroethylene with the experimental E_a=65 kcal/mol.

As can be seen, the calculated ΔDE and experimental E_a – values are rather similar. The single exception is cis-dimethylmaleat with E_a=26.5 and ΔDE=49.4 (kcal/mol); the singularized low $A=6{,}8\cdot10^5 sec^{-1}$ suggets a singlet-triplet energy potential crossing in this case.[2,3] The experimental E_a and A – values are from literature (see the review[3] for approximations).

Table 1

Experimental, E_a and calculated ΔDE activation energies for cis-trans isomerisations in gaseous phase[2,3]

Molecule	A	E_a	ΔDE
Trans-Dideuthereroethylene	$1\cdot10^{13}$	65	(65)
cis-2-Butene	$6.1\cdot10^{13}$	62,8	62,4
trans-Dichloroethylene	$4.9\cdot10^{12}$	41,9	46,8
cis-Stilbene	$6\cdot10^{12}$	42,8	45,9
cis-β-Cyanstirene	$4\cdot10^{11}$	46,6	44,2
cis-Methylcinamat	$3.5\cdot10^{10}$	41,6	39,0
cis-Dymethylmaleat	$6.8\cdot10^5$	26,5	49,4

A in sec^{-1}; Ea and ΔDE in kcal/mol. For quotations of experimental A and Ea literature data, see.[3]

For the cyclobutane → ethylene ($cC_4H_8 \rightarrow C_2H_4$) decomposition, the stretching of two opposite C-C bonds was considered as reaction coordinate[4]. The activated complex is situated at the intersection of Morse potential curves for dissociation of two C-C bonds and the 6-12 Lenard Jones potential for repulsion of two ethylene molecules[5] (corrected for the heat of reaction). This point is at 83 kcal/mol. The internal energy of normal cC_4H_8 molecule is considered as zero. The configuration interaction energy (cC_4H_8 with 2 C_2H_4) must be subtracted. According to the method of Pople[6] and with electronic repulsion integrals according to Pariser and Parr[7] this is 15 kcal/mol. The so calculated activation energy is 68 kcal/mol, rather close to the experimental 62.8 kcal/mol.

Thermal and photochemical reactivities for redox – reactions of complex oxalates of the type:

$$[Mn(C_2O_4)]^{3-} \rightarrow [Mn(C_2O_4)_2]^{2-} + CO_2 + C_2O_4^{2-} \qquad (1)$$

were discussed on the basis of potential energy diagrams for the reaction coordinates and of spectral data (for energies of fundamental and excited electronic states of the complexes).[8] The increase in redox reactivity in the series Cr^{3+}, Fe^{3+}, Co^{3+}, Mn^{3+} parallels the decrease of polarographic redox potentials (corrected for a constant spin – state) and the electroaffinity of these ions.

HMO calculations for organic molecules were performed in connection with the general problem of aromaticity. Some results concerning stability, reactivity, spectra, are described in a review.[9] One condition for aromaticity is the presence of 4n+2 pi (π) – electrons (n=0,1,2,…) which are contributed by three types of atoms, X, Y, and Z with 2,1 or 0 electrons contributed per atom respectively. An enormous number of $X_aY_bZ_c$ – molecules which fulfill the 4n+2 – pi electron condition can be imagined. The stability of such systems parallels the delocalization energy DE. This can be calculated by the HMO method, as well as the frontier orbital energies, ε_{HO} and ε_{LE} (of highest occupied and lowest empty molecular orbital). Results of such DE – calculations are listed in ref.[9] "Aromaticity constants", k_H were also defined, which express the tendency of such atoms to donate (or accept) electrons to the conjugated system.[9,10] The stability of $X_aY_bZ_c$ – molecules requires a not too high absolute value for the sum of the k_H – aromaticity constants.

With dr. Radu Vâlceanu, HMO calculations were performed for phosphorus-containing heterocycles with possible aromatic character. Four models were proposed for the participation of the P – atom to the aromatic system.[11] For 1,1–diphenylphosphabenzene, comparison of HMO results with stability and electronic spectra favour the so called Fukui model *i.e.* one π -electron, one d–orbital (d^3s–hibrid).[12] More advanced, Pariser–Parr–Pople, calculations indicate a more complex participation, of several 3d–P atom orbitals to the conjugated system.[13]

Let us also mention the application of the Goodman and Shull[14] method to the electronic (UV, Viz) spectrum of phenyl-substituted pyridine and pyrilium derivatives.[15] This method allows a semiempirical, rudimentary inclusion of configuration interaction.

Radiationless transitions correspond to transformation of the electronic energy of excited states into vibrational energy of, finally, the electronic ground state (*i.e.* – thermal energy). The results obtained in this field are given in a review, together with a general theory for this phenomenon.[16] In order that such a transition takes place, the hyperdimensional energy surface of the excited electronic state must intersect (within the multidimensional space of the nuclear – vibrational coordinates) the corresponding energy surface of the electronic ground state.[17] Coupling of the two states is produced either by spin orbit coupling (between a triplet and a singlet state)[17,18] or by terms of the time dependent Schrödinger equation neglected when this is split into an equation for electronic and respectively for nuclear movements – the Born – Oppenheimer approximation.[16]

A more detailed discussion of a radiationless transition was given for the diphenylmethylium cation[19] (I in Fig. 1), which is not fluorescent in water solution, while the more rigid molecular cation (II – Fig. 1) is luminescent.[18]

For both molecular cations (I and II), the electronic states can be constructed from the states corresponding to two phenyl rings and the CH^+ positive moiety, as described in refs.[20] and.[21] Four combinations of the functions for the two phenyl rings are possible, but only one interacts with the function for the CH^+ moiety. The ground state for I (and also II) results from the combination of the interacting C_6H_5 – functions and the function for the CH^+ moiety. The first excited state corresponds to combinations of phenyl ring functions not interacting with the CH^+ function (triple degenerate). The energy difference between the ground and excited state (calculated, about 2.0 eV) corresponds to the first electronic absorbtion band. If the two phenyl rings are torsioned at $\theta=90^o$ to the CH^+ plane, the calculated interaction becomes zero, the potential energy curves for the ground and excited states become degenerate (Fig. 2). At this point the radiationless excited to ground state transition takes place. The torsion around the C–C bonds is free in cation I, but in II, the supplementary C–C bonds with the CH_2–moiety inhibit this torsion. That explains why the diphenylmethilium cation is not fluorescent, but II is; the structurally inhibited torsion in II increases the energy of the crossing point between the fundamental and first excited electronic states.

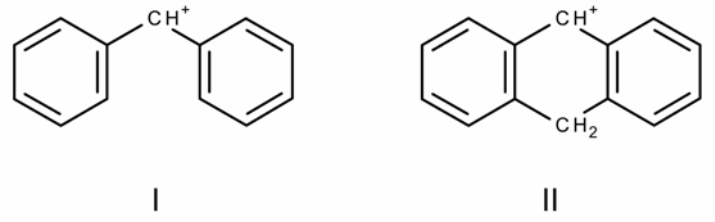

Fig. 1 – Fluorescent (II), and nonfluorescent (I) molecular cations (water solutions)[18]; I- diphenylmethylium cation; II-Anthranylium cation.

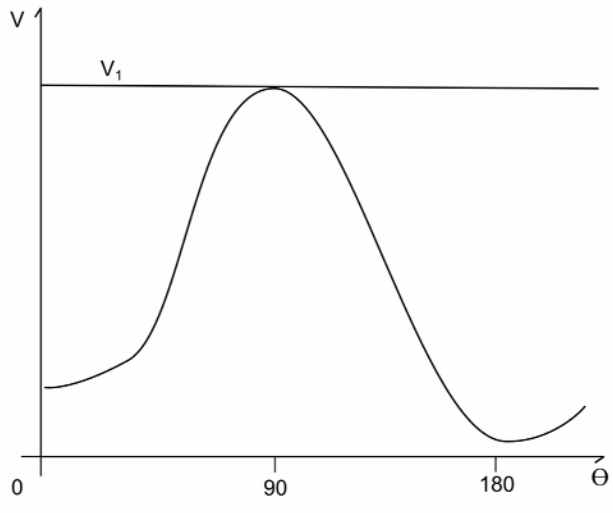

Fig. 2 – Ground state, V_o, and first excited state, V_1, potential energy curves as function of the torsional angle, θ, around the ≡C–CH^+–C≡bond[19] (in I).

Equilibria in water solution. Predictions of ΔG_d–dissociation free enthalpies for A+B↔AB type processes require calculation of hydration (free) energies, ΔG_h. We used two types of methods for the discussion of these processes.[22]

First, the (PCM)[23] – polarization continuum model which requires quantum chemistry methods for calculation of molecular charge distribution, usually by ab initio or DFT coupled with a 6-31G* basis set. This method has an iterative character: charge distribution for A, B and AB in vacuum; polarization of the surrounding water continuum (dielectric constant D=78.5); the polarized continuum perturbes the charge distributions in A, B and AB; recalculation of the water polarization; etc.

Second, the BEM boundary element method[21] - which calculates ΔG_d as sum of molecular mechanics energy terms (quantum chemistry for A, B, AB, semiempiric van der Waals, coulombic and steric strain interactions). The solvation energy ΔG_h for the participants is added (calculated by continuum dielectric model with interior D=2, surrounding water D=78.5).

Our group calculated such ΔG_d's in connection with saline bonds, a collaboration with professor O. Popescu.[25] We performed hydration ΔG_h calculations for processes of the type:

$$[ML_2]^{2-2Z} \rightarrow 2L^{Z-} + M^{2+} \tag{2}$$

in water solutions, with M^{2+}: Ca^{2+}, Mg^{2+} and L: acetate, methylsulfate, 1,2- ethandiol and 1,4 dioxan.[22]

PCM gives rather questionable quantitative ΔG_h values but indicates, clearly, the Ca^{2+} - saline bonds to be much more stable than the Mg^{2+} - saline bonds.[26] BEM results (available only for acetate complexes) indicate $(CH_3COO)_2Ca$ more stable than $(CH_3COO)_2Mg$: ΔG_d of +8.54 and 3.12 kcal/mol[27] respectively.

ΔG_d – calculations with BEM were performed for stability constants of complexes:[28]

$$[Co(NH_3)_6]^{3+} + 6H_2O \leftrightarrow [Co(OH_2)_6]^{3+} + 6NH_3 \; ; \; \Delta G_d = +21.2 \text{ kcal/mol} \tag{3a}$$

$$[Fe(NH_3)_6]^{3+} + 6H_2O \leftrightarrow [Fe(OH_2)_6]^{3+} + 6NH_3 \; ; \; \Delta G_d = +18.3 \text{ kcal/mol} \tag{3b}$$

in agreement with the stability of the first and lack of stability of the second complex; for the cobalt complex ΔG=+31.8 kcal/mol is inferred from the stability constant.

Watson – Crick base pairing energies in water solution were calculated with both the PCM[29] and the BEM method.[30] The BEM – results (free energy) are +4.32 kcal/mol for TA base paie, +4.57 kcal/mol for CG and +9.73 kcal/mol for the false TGenol – pair. If the last decrease in stability (about 5.3 kcal/mol) causes point mutations, the mutation rate should be of about 10^{-4}, within the range of 10^{-3}-10^{-6} obtained for proofreading by DNA deficient polymerase.[31]

The BEM results are more realistic than those for PCM in the above discussed work. An explanation, BEM calculates directly interaction energy terms between the central ion (M^{2+}) and the ligands (L^{z-}). In PCM the dissociation ΔG_d (about 10 kcal/mol) is calculated as difference between the large (10^5 – 10^6 kcal/mol) formation ΔG_d' s of reactants and initial, hydrated ions.

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP: MINIMAL STERIC (TOPOLOGIC) DIFFERENCE

The first QSAR–paper of our group in Timişoara was published in 1972.[32] The Multilinear Regression, MLR approach of Hansch[33] offered a good description for molecular structure and property parameters, but no adequate description for steric parameters. Our MSD (minimal steric difference) parameter,[34] later called MTD,[35] was a step forward in this direction. The MSD_i, minimal steric difference, between a ligand molecule L_i and a standard, S_o, is the number of nonsuperposable (nonH) atoms when L_i is superposed upon S_o,[34] The standard, S_o, is very often the most active molecule in the series considered for QSAR. The MSD_i – values (for each L_i molecule) are considered as "structural" parameters in a QSAR.

In the MTD-version,[36,37] the superposition of the i =1,2,…., N molecules L_i of the series for QSAR yields the hypermolecule. This is a network with j =1,2,…., M vertices which correspond to atomic positions of the superposed L_i molecules. In each molecule (ligand) L_i, vertex j of the molecule can be either occupied or empty, x_{ij}=1 or x_{ij}=0. The minimal steric difference, MTD_i, becomes:

$$MTD_i = s + \sum_{j=1}^{M} \varepsilon_j x_{ij} \tag{4}$$

The M vertices (when occupied) can be either beneficial, detrimental or neutral with respect to R-L_i affinity. The corresponding ε_j values are -1, +1 or 0, which are determined by a special optimization program (s is the total number of vertices with $\varepsilon_j = -1$).[36c]

With adoption of the PLS technique, a new version, MTD-PLS was developed,[38] which allows consideration of a larger number of structural variables (with respect to the N-numbers of Y_{exp} – experimental L_i activities) than the MLR technique.[33] The correlational equation for the caculated $\hat{Yi}$ activity of L_i becomes:

$$\hat{Yi} = a_o + \sum_{j=1}^{N} (a_{jv} V_{ij} + a_{jH} H_{ij} + a_{jP} P_{ij} + a_{jA} A_{ij} + a_{jD} D_{ij}) \quad (5)$$

V_{ij}, H_{ij}…, etc. are increments for the atom X (XH_n – group) in L_i which occupies vertex j, for volume, hidrophobicity, polarizability, electric charge and hydrogen bond acceptor or donor capacity. In order to have realistic values for correlation coefficients, *i.e.* volume increments detrimental because of steric misfit, hydrophobic interactions always beneficial, etc. certain restrictions are to be imposed on the a_{jv}, a_{jh}, etc. coefficients, namely:

$$a_{jv} \leq 0;\ a_{jH} \geq 0;\ a_{jP} \geq 0 \quad (6)$$

The columns of variables for which the $a_{j\mu}$- conditions (6) are not satisfied are to be eliminated (by the computer programs).[39] For example, in an MTD-PLS approach to the AchE-catalysed hydrolysis rates of CH_3COOR esters (N=25) from the initial MTD-PLS with N=25 molecules and 49 structural variables with q^2= 0.597, a final model is obtained[39] with N=22 molecules, and 41 variables (V_{ij}, H_{ij}, S_{ij}) with q^2= 0.796. For more detailed considerations of $a_{j\mu}$- coefficients, see paper.[40]

QSAR for carcinogenicity. An interesting MTD-QSAR application is given in ref.[41] Carcinogenicities for three different carcinoma types of various PAH's were given by three authors. Jerina[41] classifies N_1= 11 various PAH'S in v.a. = very active, m.a. = moderately active and i = inactive. Slage *et al*[44] and Higgins *et al*[43] give for m.a. alkyl and alkoxy PAH derrivatives more specific carcinogenicity values (N_2= 29 sarcoma inducing PAH's,[43] N_3= 13 papilloma inducing[44]). N_1, N_2, N_3 are the numbers of (different) PAH's studied by each group.

For QSAR purposes we considered carcinogenic activities of v.a. compounds with Y=+1.5 and Y=-0.5 for inactive compounds.[41] As structural parameters, following some considerations of Jerina,[42] we consider certain cation destabilization energies, DE, as one structural parameter. We calculated the corresponding DE–values by the ω-HMO method.[41] The corresponding correlation coefficient with DE, for two groups of compounds mentioned before, are r_2= 0.573 (N_2=29), r_3=0.792 (N_3=13). Adition of the topologic average distance conectivity,[45] j, increases the correlations to r_2(DE,j)=0.819 (sarcoma induction) and respectively r_3(DE,j)=0.826 (papilloma induction)[41]. The MTD-method was applied to the combined series of sarcoma and papilloma inducers ($N=N_1+N_2+N_3=42$). For MTD, the PAH'S are superposed such that the position of the six-membered epoxydised ring is the same for all N=42 inducers. For the QSAR's with DE and MTD, r_2(DE,MTD)=0.840 is obtained for sarcoma induction and r_3(DE, MTD)=0.824 for papilloma induction. With the DE plus MTD values for all $N_1+N_2+N_3=53$ potentially carcinogenic PAH's and derivatives, 42 are correctly classified in the v.a., m.a., and i.-classes and there are no false attributions between the extreme v.a. and i.-classes.[41]

Thus, albeit with rather unorthodox definitions of "experimental" carcinogenicities, rather acceptable predicted attributions to the v.a., m.a., and i.-classes are obtained.

SPECIFICITY OF BIOLOGICAL PROCESSES

High specificity is related to molecular size. In classical analytical chemistry, small anions, such as sulphide (S^{2-}) or carbonate (CO_3^{2-}) precipitate large groups of cations; chelating agents (EDTA) are more specific, while repressor proteins bind specifically to a single small DNA region, the repressor. The general situation can be presented as follows:[46]

$$R_o + L_i \leftrightarrow C_{oi};\ i=1,2,...,N; \quad (7)$$

C_{oo} is the enzymatic reaction, specific cell activity.

The R_o-L_i interaction can be considered as a series of parrallel equilibria or kinetic processes, or, especially if cell or membrane surfaces are implied, as precipitation equilibria.

If precipitation equilibria are considered, the conditions for correct functioning will be:

$$[R_o][L_o] \geq P_{oo}\,;\ [R_o][L_i] < P_{oi}\,,\ i=1,2,...N;\ P_{oi}= \exp(-\Delta G_{io}/RT) \tag{8}$$

Here, P_{oo} and P_{oi} are solubility products, and ΔG_{io} the R_o-L_i affinities.

The equilibrium considerations of eq. (8) produce some precision (high specificity) molecular size relations with some simplifying assumptions and aproximations. Consider the interacting R_o-L_i pair as linear polymers of α-types of monomers with n-monomers (of R_o and L_i) in direct contact. Consider also a "complementarity" relation, perfectly respected in the R_o-L_o contact, and the ΔG_{oo}- ΔG_{oi} affinity decrease proportional to the number υ_{oi} of false conctacts, *i.e.*:[46a]

$$\Delta G_{oo}- \Delta G_{oi} = \upsilon_{oi}\, \Delta g \cong \bar{\upsilon}\, \Delta g \tag{9}$$

Combinatorial considerations yield relations between the size, n, of the contact region, α,υ and Δg, and the (volume or surface) concentrations (activities) of correct and false, L_o and L_i – potential ligands:[46a,b]

$$\bar{\upsilon} \cong \frac{2{,}3RT}{\Delta g} \lg \frac{[L_{f\max}]}{[L_o]} \tag{10a};$$

$$n > \underset{\sim}{\bar{\upsilon}} - 1 + \frac{(\bar{\upsilon}-1) + \lg N}{\lg \alpha} \tag{10b}$$

Relationship similar to (10a) and (10b) are obtained when parrallel, usual (non highly cooperational) solution equilibria (in R_o-L_i) interactions are considered.[46a] $[L_{fmx}]$ is the largest concentration (volumic, surface, activity) of a false L_i-ligand in the system.

Concerning Δg, an inspection of experimental data[47] yields a mean value for the Δg affinity decrease of $\Delta g \cong 2.0\text{-}2.5$ kcal/mol, when in the perfectly "complementary" R_o-L_o pair, an aminoacidic residue (in the L_o contact region) is substituted by another residue.[48] For adition or substraction of an (nonH) atom in the L_o– contact region, inspection of some QSAR's based on MTD indicate a decrease of about 1.0 kcal/mol in the R_o-L_o affinity.[49]

Equations (10a) and (10b) can be used to calculate the size of the Lac operator gene in E.coli (more exactly the size of the nucleotidic operator region interacting with the Lac-repressor protein). We obtained n>27 base pairs for the nucleotidic operator region.[50] Sadler and Smith,[51] under the assumption of a binomial repartition of nucleotides in the E.coli genome, obtained n=18 base pairs for this size. Experimental studies of Gilbert and Maxam[52] indicate n= 27 base pairs for the Lac operator gene.

As remarked at the end of the quantum chemistry part of this paper, false $T_{enol}G$ pairing could produce an 10^{-4} rate for point mutations – (10^{-3}...10^{-6} for proofreading by DNA deficient polymerase[31]). The real, much reduced, 10^{-10} per base pair mutation rate is obtained, according to Hopfield,[53] by **kinetic proofreading**, which is a sort of sequential control. After inclusion in the new DNA strands, the new base pairs are tested by a second enzyme which rejects the false base pairs.

Immune response is an intricate process which cannot be reduced to a single recognition process.[54] Namely, immune attack (response) takes place against at least one antigen presented by the assaulting pathogen, but against neither of the about $N=5\cdot10^7$ overlapping short peptides (of a given size) within the proteins coded by the host genome. The antigen (immunogen) is recognised by a certain T_H(helper) clone and also by a CTL or B–cell clone. Only the interaction between both recognitions, by T_H and CTL or T_H and B, produces the immune response (even if some self -antigenic determinants are subject of only one of these recognition processes).

For some mathematical models for immune response see.[55-59]

Similar ideas concerning parallel equilibria in immune response or concerning combinatorial mathematics implications were put forward by Volkenshtein and Eliashevich,[60] and by Thomas[61a] and by Conaughy and McCarthy.[61b]

MATHEMATICAL MODELS FOR GENE AND CELL CYCLE REGULATION

Mathematical biology is indebted to the work of scientists like A. J. Lotka, R. A. Fisher, Vito Voltera (see for example[62]). The biological problem is transposed into a system of time dependent differential equations and their discussion. The trigger of interrelated operons of the present author[63] and of Tsanev and Sendov,[64] in the middle sixties, were among the first mathematical models related to cell biology.

Triggers of interrelated operons, based on negative control, imply two genes which synthetise the repressor for each other.[63,64] Transcribed in the language of chemical kinetics, they yield a system of differential equations which, in certain conditions, can have two steady states.[65] Positive control, an operon activated by an operator (gene) activator synthetised by a gene of the same operon, can function also as a trigger with two steady states (active or inactive in protein synthesis).[66] Oscillatory behaviour can also appear, as in a computer simulation of a system of two interacting genes (p 53 and mdm2).[67]

Cell cycle models are based on a mechanism that starts DNA replication, considered to be followed, authomatically, by other processes conducting to cell division. Such a model, for unicellular organism, based upon a threshold dTTP concentration to start DNA synthesis (and a product inhibited dTTP synthesis) gives a linear dependence of mean cell volume upon cell cycle duration[68] and is observed only for slow growing bacteria (as quoted by [69]).

The more usual situation, mean cell volume constant – not dependend upon replication rate, is obtained if the start for cell replication is given by the moment when the complementary DNA quantity, required for chromosome doubling, is synthetised.[70]

MAIN CO-WORKERS-SUPPLEMENTARY INFORMATION

The co-authors whose names appear most frequently in the list of my about 350 published papers are A. T. Balaban, Claude Nicolau and Ilie Bădilescu. The last two were also my fellow students at the Faculty of Chemistry in Bucharest.

A. T. Balaban, member of the Romanian Academy, is today's best known Roumanian organic chemist. Our first common publication[71] appeared in 1962, the last[72] in 1986.

With Claude Nicolau, the cooperation was related to physical chemistry methods in biomedical studies, such as electronic paramagnetic resonance,[73] but also other items. The first Roumanian treatise concerning molecular biophysics[74] was the result. Our cooperation ended when he left Roumania for USA. He is a honorary member of the Roumanian Academy.

I and Ilie Bădilescu co-authored 11 publications, mostly on QSAR and MTD, but also on decomposition reactions of diazoderivatives and diazonium salts, considered from the point of view of correlational diagrams between electronic states of the reactant and the reaction products.[75] My single experimental paper – a study on sensibility of germination of seeds of different ploidies towards alkylating agents, is based[76] on cooperation with him and my wife (Stela Botiş-Simon). Ilie Bădilescu was a dedicated organic chemist. His main interests were heterocycles of medium size, cyclisations, transpositions with ring enlargements. Concerning the interests of Ilie Bădilescu and Simona Vaida-Bădilescu (his wife), we may quote studies of hydrogen bond strengths in organic compounds by infrared spectroscopy,[77] ring size cyclization of butyramide derivatives,[78] cyclization of ring substituted phenoxybutyric acid derivatives[79] and Beckman rearangements.[80] After 1985 they lived in Canada where Ilie Bădilescu was nominated as an organic chemistry professor at the Université de Moncton (New Brunswick county) in 1987. He died, rather prematurely, in 1998.

CONCLUSIONS

Less invention and developments of new domains – more interconnections among different domains; this is a characteristic of the authors research.

As scientometric data – 350 published papers, a total of about 1200 quotations – perhaps about 600 nonselfquotations (if also non ISI publications are included). A calculated h=15 Hirsch factor. The most cited paper concerns charge transfer spectra in pyrylium iodides, with A. T. Balaban,[81] (44 quotations), followed

by mapping of DHFR receptor sites[37] with 41 quotations; in molecular biology applications – possible oscillations in p 53 – mdm2 gene interactions,[57] 36 quotations.

The research domains – very varied, but with several interconnections. Quantum chemistry – applications to spectra and reactivity of organic compounds; unimolecular reactions and processes (with the late I. G. Murgulescu); QSAR – the MTD method; mathematical models for gene and cell cycle regulations.

In quantum chemistry, my main contributions are in the domain of applications and limits for such applications. Several papers on spectra and reactivity of organic compounds – but also inorganic. An inquiry on the applicability of ab initio and semiempiric methods; in my times I preferred the semiempiric ones. One should be careful and prefer direct, approximate computations of interactions relatively to ones which refer to small differences between large computed numbers.

In QSAR, my main contribution, the MTD – method is perhaps the most intuitive semiempirical method for steric effects. It attained a rather large applicability but more elaborate computer based methods are nowadays prefered. In applications to molecular biology, perhaps an attempt to a general theory of specific interactions and construction of realistic mathematical models for cell regulation, based upon physical chemistry.

I must thank many collaborators, without their contribution the results obtained, even if not very impressive, would not have been possible. Among my teachers, my mathematics professor, Arno Kahane; for physical chemistry – professor I. G. Murgulescu, Tatiana Oncescu. Of the collaborators, A. T. Balaban in first rank, and also Ilie Bădilescu; in Timişoara A. Chiriac, G. I. Mihalaş, Ştefan Holban and several others. I apologize for my limited and imperfect memory. My elder colleague, the late Henry Kehiaian must also be mentioned, for advice in audacity and, sometimes, in risking not to obey advice. I am grateful to my parents, who, several decades ago, in difficult times, invested their last resources in my professional, but also general – cultural education; and to my family, my wife who had to accept an often absent minded father and husband.

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