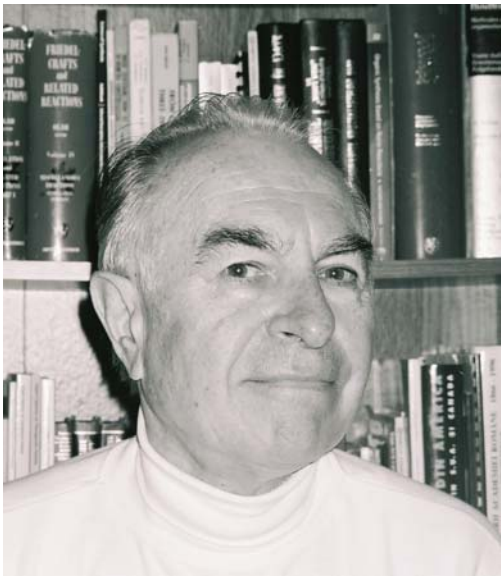
Professor Alexandru T. Balaban

A Tribute



Alexandru T. Balaban was born in Timisoara, Romania, on April 2, 1931. In 1959 he obtained his Ph. D. under the supervision of Costin D. Nenitzescu, the founder of the Romanian school of organic chemistry, followed by a D.Sc. in 1974. He also became a Dipl. Radiochemist in 1957, and in 1961 he founded the laboratory for Isotopically Labeled Compounds at the Institute of Atomic Physics in Bucharest.

From 1956 until 1999 (except for the three years when he was in Vienna with the International Atomic Energy Agency), Professor Balaban taught basic organic chemistry, as well as advanced topics, to many generations of students at the Bucharest Polytechnic University. Here he advised more than 40 Ph. D. students, and hosted visiting researchers from Britain, USA, USSR, Greece and Turkey. Since 2000 he has continued his teaching and research as a tenured Professor of Chemistry at the Texas A&M University in Galveston.

Professor Balaban is the most cited organic chemist for research performed in Romania. In D.A. Pendlebury's *List of the Most Cited Chemists (1981-1997)*, there are more than 1600 citations for his papers, with more than 500 citations for papers published after 1981 (not including citations of books). Several of his papers have been cited over 100 times each. His publications include 9 authored books, 7 edited books, over 50 chapters in books edited by other authors, over 600 papers published in peer-reviewed journals and 26 patents, three of which are USA patents.

Among Professor Balaban's diverse research interests, I will mention some in which he made landmark contributions:

Experimental organic and bio-organic chemistry

Pyrylium salts. The Balaban-Nenitzescu-Praill synthesis of pyrylium salts was a serendipitous discovery during Professor Balaban's Ph.D. work. Diacylation of olefins has proved over the years to be the best method for the synthesis of alkyl-substituted pyrylium salts with identical substituents in positions 2 and 6. New methods for the syntheses of furans, pyrazolines, diazepines, indolizines and oxazolines, based on the reactions of pyrylium salts with nucleophiles, were developed by Balaban and his co-workers. Dimroth, Schroth and Dorofeenko discovered other reactions in this area. Together with Schroth and Dorofeenko, and also with Dinculescu, Fischer, Koblik and Mezheritskii, he published in 1982 the first monograph on pyrylium salts, as a supplementary volume in the series "Advances in Heterocyclic Chemistry" edited by A. R. Katritzky. A comprehensive review on pyrylium salts (with Professor W. Schroth) was published in 1996 in the Houben-Weyl series "Methoden der Organischen Chemie". For the revised, expanded and up-dated English version of this review in "Science of Synthesis: Houben-Weyl Methods of Molecular Transformations" he collaborated with his son, Dr. Habil Teodor-Silviu Balaban. Studies on the syntheses and properties of pyrylium salts followed throughout his career. These compounds were found to form charge-transfer salts with iodide and pseudo-halogen anions. Reaction with amines yielded pyridinium salts which displayed hindered rotation about the N^{+}–C bond. His current research interests in the area deal with pyridinium salts as ionic liquids and more recently with pyridinium cationic lipids as gene transfer agents, concerning which, Professor Balaban and his co-workers at the Texas A&M University in Galveston filed a patent.

Stable nitrogen free radicals. Professor Balaban discovered that in addition to steric shielding, the presence of both an electron donor and an electron acceptor attached to the same nitrogen atom (the "push-pull" effect), provided stable aminyl radicals. Stable hydrazyls are a particular case of such aminyls. Barriers to rotation in some aminyl radicals were then studied by EPR spectroscopy. Hyperfine coupling constants in the EPR spectra were assigned by ^{15}N labeling.

Nitric oxide donors. While in Bucharest, he showed that nitric oxide (NO) can be spin-trapped by nitrosoarenes yielding cupferron derivatives. Further studies at Galveston, now patented world-wide, developed new NO donors, and solutions of NO in fluorocarbon emulsions. Two gels which, on mixing, release NO can be used for treating wounds and burns.

Catalytic isomerizations of polycyclic aromatic hydrocarbons. Degenerate isomerizations, for which Balaban coined the term "automerizations", were demonstrated for phenanthrene in melts of $AlCl_3$·NaCl at 200 °C, by ^{13}C labeling in various positions.

Homogeneous catalysis under acid conditions. The results of investigations of the Scholl and other reactions with synthetic utility catalyzed by Brønsted and Lewis acids, were published and then reviewed in two chapters of Olah's monograph "*Friedel-Crafts and Related Reactions*".

Isotopically labeled compounds. In the process of elucidating reaction mechanisms by isotopic labeling, Professor Balaban devised new syntheses of labeling organic molecules with deuterium, tritium, and ^{14}C. The reversibility of the Friedel-Crafts aliphatic acylation was demonstrated by ^{14}C labelling; in these studies a new method for the synthesis of labeled alkanes was developed. Deuteration in the alpha positions of alkyl groups attached to positions 2 and 4 of the pyrylium salts occurs readily by slight heating in D_2O. Structural features were utilized to

perform the reaction regioselectively. Tritiation of aromatic and aliphatic compounds was performed with aluminum chloride, which formed a superacid with traces of tritiated water.

Theoretical chemistry areas and drug design

Chemical applications of graph theory. Professor Balaban is a pioneer in the application of graph theory to chemistry. In collaboration with Professor Frank Harary he developed dualist graphs of polycyclic aromatic hydrocarbons which allowed the complete enumeration, coding and nomenclature of such systems. He introduced the first reaction graphs and later reviewed this topic in a book chapter. In a collaboration with Professor Paul von Ragué Schleyer, he developed a nomenclature system for diamondoid hydrocarbons, also based on dualist graphs, adopted by the recent discoverers of such hydrocarbons in the solid deposits of natural gas pipelines.

Valence isomers of annulenes and their derivatives. Professor Balaban described the procedure allowing the first exhaustive enumeration of annulene valence isomers, and published the first 3-volume monograph on these valence isomers.

Topological indices and other molecular descriptors. In his work on molecular modeling and drug design via QSAR and QSPR studies, Professor Balaban introduced many new topological indices; one of these indices (the average distance-sum connectivity, denoted by *J*) is known as the Balaban index, and is used successfully in drug design.

Carbon nets. Professor Balaban published in 1968 the first paper on possible alternative carbon nets, different from diamond or graphite, and more recently continued these studies in joint papers with R. Hoffmann and with colleagues from the Texas A & M University at Galveston.

Theoretical invariants for fullerenes, graphitic cones and carbon nanotubes. Professors Balaban and Klein predicted the existence of graphitic cones before they were observed, and published studies on graph-theoretical characteristics that determine uniquely the structure of fullerene cages. Professor Balaban imagined and calculated nanotubes with heteroatoms at their ends, thus avoiding dangling bonds; such systems were prepared experimentally in 1999.

Cages. In graph theory a cage is the minimal highly symmetric regular graph of degree three whose minimal circuit (girth) has a given number of points. As an extension to his studies of reaction graphs, he discovered the trivalent cages with girth 10 and 11, known as Balaban cages.

It is interesting that Professors Balaban and Katritzky, whose friendship started when they first met in Bucharest in 1960, have several areas of mutual interest, and collaborated in some of them resulting in joint publications in the following areas: (i) push-pull stabilization of free radicals, named “merostabilization” by Professor Katritzky; (ii) reactions of pyrylium and pyridinium salts, developed by Professor Katritzky into a synthetic method for replacing an amino group by other functionalities; (iii) QSAR using various molecular descriptors, culminating with the CODESSA program developed by Professor Katritzky’s group; (iv) aromaticity, which involves an amazing coincidence in that Professors Balaban and Katritzky proposed almost identical notation completely independently (this story is described in detail in their joint review published recently in *Chem. Rev.* **2004**, *104*, 2777-2812).

Of his service to the international community one must mention his appointment to the International Atomic Energy Agency, 1967-1970, where he devised international standards for the quality control of pharmaceuticals and organized several international meetings.

He is member in the editorial boards of 12 journals: *Polycyclic Aromatic Compounds,* USA; *Organic Preparations and Procedures International,* USA; *Advances in Heterocyclic Chemistry,* USA; *Fullerene Science and Technology,* USA; *Communications in Mathematical Chemistry*, Germany; *SAR and QSAR in Environmental Research,* France; *Journal of Radioanalytical and Nuclear Chemistry,* Holland; *Heterocyclic Communications*, England*; Scientometrics,* Hungary; *Revista de Chimie - Bucharest,* Romania); *Central European Journal of Chemistry*, The Czech Republic; *Internet Electronic Journal of Molecular Design* (USA). Past memberships include: *Journal of Chemical Information and Computer Sciences*, USA; *Journal of Labelled Compounds and Radiopharmaceuticals,* USA; *Journal of Computational Chemistry*, USA; *Journal of Mathematical Chemistry,* Canada; *Acta Chimica Hungarica – Models in Chemistry*, Hungary; *Bulletin des Sociétés Chimiques Belges*, Belgium.

Professor Balaban has served the Romanian scientific community as a member of the Romanian Academy since 1963 and as vice-president between 1995 and 1998. In this capacity, he undertook for the first time in Romania the distribution of research grants based on peer review and he organized several international conferences and workshops in Romania. He was the Head Editor of the Romanian Academy of Science's chemical journals published in English (*Revue Roumaine de Chimie*, and *Roumanian Chemical Quarterly Reviews).*

He has given invited lectures and lecture tours in USA (1982, 1993, 1994, 1996), Canada (1990, 1992), UK (1969), Israel (1981), Germany (1965, 1973, 1976), India (1964), Belgium (1972), and Italy (1994).

Professor Balaban has also been the recipient of numerous distinctions and awards for his outstanding contributions to chemistry: the Herman Skolnik Award of the Division of Chemical Information of the American Chemical Society, 1994; Dr. Honoris Causa, Univ. Timisoara, Romania, 1997; Romanian Academy Prize, 1962.

As a former Ph. D. student, I admired Professor Balaban not only for his achievements in chemistry and science in general, but also for his interests in any given topic from cartoons to science fiction literature. He speaks English, French and German fluently and has lectured in Russian and Spanish. Leaving aside his high research standards that he imposed on his students, an important aspect of his legacy is that he always taught us not to give up hope. A great number of his students followed his diligence and are now part of the international scientific community.

For his upcoming 75th birthday in April 2006, the colleagues from Romania and abroad, his many friends and his former students, send their wishes for many happy and productive years.

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Selected Publications

1. Balaban, A. T. Ed. *Chemical Applications of Graph Theory*, Academic Press: London, 1976, p 389.
2. Balaban, A. T. Ed. *From Chemical Topology to Three-Dimensional Geometry*, Plenum Publishing Corporation: New York, 1997, p 420.
3. Balaban, A. T.; Carabateas, E. N.; Tanasescu, F. A. *Science and Technology Management*, NATO Science Series (Series 4: Science and Technology Policy, Vol. 22), Proc. of NATO Advanced Research Workshop (Sinaia, Romania, May 20-24, 1997). IOS Press: Series 4, Amsterdam, Vol. 22, 1998, p 243.
4. Devillers, J.; Balaban, A. T. Ed. *Topological Indices and Related Descriptors in QSAR and QSPR*, Gordon and Breach: The Netherlands, 1999, p 811.
5. Balaban, A. T.; Dinculescu, A.; Dorofeenko, G. N.; Fischer, G. W.; Koblik, A. V.; Mezheritskii, V. V.; Schroth, W. *Pyrylium Salts. Syntheses, Reactions and Physical Properties*, *Advances in Heterocyclic Chemistry*, Suppl. Katritzky, A. R. Ed. Academic Press: New York, 1982; Vol. 2, p 454.
6. Balaban, A. T.; Banciu, M.; Ciorba, V. *Annulenes, Benzo-, Hetero-, Homo-Derivatives and Their Valence Isomers*, CRC Press: Boca Raton, Florida, 1986, Vol. 3, p 686.
7. Balaban, A. T.; Nenitzescu, C. D. *Dehydrogenating Condensations of Aromatics (Scholl and Related Reactions)*, In *Friedel-Crafts and Related Reactions*, Olah, G.A. Ed. Wiley-Interscience: New-York, 1964; Vol. 2. pp 979-1047; Nenitzescu, C. D.; Balaban, A. T. *Aliphatic Acylation*, In the same book, Vol. 3, pp1033-1152.
8. Rouvray, D.H.; Balaban, A.T. *Chemical Applications of Graph Theory*, In *Applications of Graph Theory*, Wilson, R. J.; Beineke, L. W. Eds; Academic Press: London, 1979, pp 177-221.
9. Balaban, A. T. *Steric versus electronic components of secondary deuterium effects depend on the size of electrophilic probes*, In *Water and Ions in Biological Systems*, Proc. 2rd Internat. Conf. Bucharest, 1982 Pullman, A.; Vasilescu, V.; Packer, L. Eds; Plenum Press: New York, 1985; pp 655-663.
10. Balaban, A. T. *Pyrylium salts as useful synthons*, In *Organic Synthesis: Modern Trends Proc. 6th IUPAC Internat. Symp. On Organic Synthesis*, Moscow, Ed. Chizov, O.
11. Balaban, A. T. *Reaction graphs*, In *Graph Theoretical Approaches to Chemical Reactivity*, Bonchev, D.; Mekenyan, O. Ed., Kluwer Academic Publishers: Dordrecht, Netherlands, 1994, pp137.
12. Balaban, A. T. *Trimethylpyrylium* In Vol. 7, pp 5224; *Triphenylpyrylium* In Vol. 8, pp 5407-5411, monographs in *Encyclopedia of Reagents for Organic Synthesis (EROS)*, (L.A. Paquette, Ed., Wiley: New York, 1996; *2,6-Di-tert-butyl-4-methylpyridine*, EROS on line, 2004.

13. Ivanciuc, O.; Balaban, A. T. *Graph theory in chemistry* In *Encyclopedia of Computational Chemistry* Schleyer, P. V. R.; Allinger, N. L.; Clark, T.; Gasteiger, J.; Kollman, P. A.; Schaefer, H. F.; Schreiner, P. R. Eds., Wiley: Chichester, 1998; pp 1169.
14. Balaban, A. T. *Theoretical investigation of carbon nets and molecules* In *Theoretical Organic Chemistry* Parkanyi, C. Ed. Elsevier: Amsterdam, 1998, pp 381.
15. Balaban, A. T. *QSAR and computational methods in drug discovery* In *Encyclopedia of Analytical Chemistry*, Meyers, R. A. Ed. Wiley: Chichester, 2000, Vol. 8, pp 7288.
16. Balaban, T. S.; Balaban, A. T. *Pyrylium Salts*. In *Science of Synthesis; Houben-Weyl Methods of Molecular Transformations*, Georg Thieme Verlag: Stuttgart, 2003; pp 11-200.
17. Balaban, A.; Birladeanu, L.; Bally, I.; Frangopol, P. T.; Mocanu, M.; Simon, Z. *Tetrahedron,* **1963**, *19*, 2199: Preparation and spectra of *para*-substituted 2,5-diphenyloxazoles (Aminoketone synthesis. VI).
18. Balaban, A. T.; Bedford, G. R.; Katritzky, A. R. *J. Chem. Soc.,* **1964**, 1646: The nuclear magnetic resonance of heterocyclic systems. Part I. Pyrylium salts.
19. Balaban, A. T.; Nenitzescu, C. D. *Org. Synth.* **1964**, *44*, 98: 2,4,6-Trimethylpyrylium perchlorate. Reprinted in Org. Synth., 1973; Coll. Vol. 5, 1106.
20. Balaban, A. T.; Halls, P. J.; Katritzky, A. R. *Chem. and Ind.* **1968**, 651: Stable radicals from 1-hydroxybenzimidazole-3-oxides.
21. Balaban, A. T. *Rev. Roum. Chim.* **1971**, *16*, 725: Stable nitrogen free radicals.
22. Balaban, A. T. *J. Combinatorial Theory, Ser. B* **1972**, *12*, 1: A trivalent graph of girth ten.
23. Balaban, A. T.; Boulton, A. J. *Org. Synth.* 1973; Coll. Vol.5, 1112: 2,4,6-Trimethyl-pyrylium tetrafluoroborate.
24. Robinson, R. W.; Harary, F.; Balaban, A. T. *Tetrahedron* **1976**, *32*, 355: The number of chiral and achiral alkanes and mono-substituted alkanes.
25. Balaban, A. T.; Von, P.; Schleyer, R. *Tetrahedron* **1978**, *34*, 3599: Systematic classification and nomenclature of diamond hydrocarbons. 1. Graph-teoretical enumeration of polymantanes.
26. Balaban, A. T. *Pure Appl. Chem.* **1980**, *52*, 1409: Is aromaticity outmoded?
27. Balaban, A. T. *Pure Appl. Chem.* **1982**, *54*, 1075: Challenging problems involving benzenoid polycyclics and related systems.
28. Balaban, A. T. *Chem. Phys. Lett.* **1982**, *80*, 399: Highly discriminating distance-based topological index.
29. Von, P.; Schleyer, R.; Kos, A. J.; Pople, J. A.; Balaban, A. T. *J. Amer. Chem. Soc.* **1982**, *104*, 3771: Carbenium-carbonium structure H_2C^+-CH_4^+, for the ethane dication.
30. Caproiu, M. T.; Elian, M.; Grecu, N.; Negoita, N.; Balaban, A. T. *J. Chem. Soc. Perkin Trans. II* **1983**, 591: Factors affecting stability and equilibria of free radicals. XI. 1-Benzoyl-2,2-bis-(3,5-di-t-butyl-phenyl)-hydrazyl and its temperature-dependent ESR spectra.
31. Balaban, A. T. *Pure Appl. Chem.* **1983**, *55*, 199: Topological indices based on topological distances in molecular graphs.

32. Caproiu, M. T.; Negoita, N.; Balaban, A. T. *Tetrahedron* **1983**, *39*, 3943: Factors affecting stability and equilibria of free radicals. XII. Capto-dative diarylaminyls with
33. Roussel, C.; Balaban, A. T.; Berg, U.; Chanon, M.; Gallo, R.; Klatte, G.; Memiaghe, J. A.; Metzger, J.; Oniciu, D.; Pierrot-Sanders, J. *Tetrahedron* **1983**, *39*, 4209: Gear effect. X. Conformational aspects of the positive or negative buttressing effects of methyl groups: polymethylpyridines.
34. Balaban, A. T.; Filip, P.; Balaban, T. S. *J. Comput. Chem.* **1985**, *6*, 316: Computer program for finding all possible cycles in graphs.
35. Balaban, A. T. *J. Chem. Inf. Comput. Sci.* **1985**, *25*, 334: Applications of graph theory in chemistry.
36. Balaban, A. T. *Comput. and Maths. with Applic.* **1986**, *12B*, 999: Symmetry in chemical structures and reactions. Reprinted In: "*Symmetry Unifying Human Understanding*", Hargittai, I., Ed.; Pergamon Press: New York, 1986; p. 999.
37. Balaban, T. S.; Balaban, A. T. *Tetrahedron Letters* **1987**, *28*, 1341: Δ^3-Dihydropyrans and tetrahydropyrans by reduction of pyrylium salts with sodium borohydride in acetic acid.
38. Merz, K.M.; Hoffmann, R.; Balaban, A. T. *J. Amer. Chem. Soc.* **1987**, *109*, 6742: 3,4-Connected carbon nets: through-space and through-bond interactions in the solid state.
39. Balaban, A. T.; Gheorghiu, M. D.; Schiketanz, A.; Necula, A. *J. Am. Chem. Soc.* **1989**, *111*, 734: Catalytic automerization of phenanthrene.
40. Balaban, A. T. *Computers Math .Applic.* **1989**, *17*, 397: Carbon and its nets. Reprinted In "*Symmetry II"* Hargittai, I., Ed.; Pergamon Press, Oxford, 1989; 416.
41. Balaban, A. T. *Annals Discrete Math.*, **1993**, *55*, 109: Solved and unsolved problems in chemical graph theory; reprinted in "Quo Vadis, Graph Theory?" Gimbel, J.; Kennedy, J. W.; Quintas, L. V., Eds; North Holland: Amsterdam, 1993.
42. Balaban, A. T. *Math. Chem. (MATCH)* **1993**, *29*, 3: Confessions and reflections of a graph-theoretical chemist.
43. Balaban, A. T. *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 398: Local vs. global (i.e. atomic vs. molecular) numerical modeling of molecular graphs.
44. Balaban, A. T.; Klein, D. J.; Liu, X. *Carbon* **1994**, *32*, 357: Graphitic cones.
45. Balaban, A. T. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 339: Chemical graphs: looking back and a glimpse ahead.
46. Balaban, A. T. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 645: From chemical topology to 3D geometry.
47. Balaban, A. T.; Babic, D. *Math. Reports (Bucharest)* **2000**, *2*, 269: Details about a (3, 11)-cage on 112 vertices.
48. Balaban, T.; Rücker, C. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1145: Using protochirons for three-dimensional coding of certain chemical structures.
49. Ilies, M. A.; Seitz, W. A.; Caproiu, W. T.; Wentz, M.; Garfield, R. E.; Balaban, A. T. *Eur. J. Org. Chem.* **2003**, 2645: Pyridinium-based cationic lipids as gene transfer agents.

50. Balaban, A. T.; Plavsic, D.; Randic, M. *Chem. Phys. Lett*. **2003**, *379*, 147: DNA invariants based on nonoverlapping triplets of nucleotide bases.
51. Balaban, T.; Ghiviriga, I.; Czerwinski, E. W.; De, P.; Faust, R. *J. Org. Chem.* **2004**, *69*, 536: Simple synthesis of a weak nucleophilic base (4-ethyl-2,6-diisopropylpyridine) evidencing a double Janus group effect.
52. Balaban, T.; Randic, M. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1701-1707: Partitioning of π-electrons in rings of polycyclic conjugated hydrocarbons. Part 5. Nonalternant compounds.
53. Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777: Aromaticity as a cornerstone in heterocyclic chemistry.
54. Randic, M.; Zupan, J.; Balaban, A. T. *Chem. Phys. Lett.* **2004**, *397*, 247: Unique graphical representation of protein sequences based on nucleotide triplet codons.
55. Ilies, M.A.; Seitz, W.A.; Ghiviriga, I.; Johnson, B.H.; Miller, A.; Thompson, E. B.; Balaban, A. T. *J. Med. Chem.* **2004**, *47*, 3744: Pyridinium cationic lipids in gene delivery: a structure-activity correlation study.