Professor Nikolai Zefirov

A Tribute

This special issue of Arkivoc is to celebrate the 70th anniversary of the birth of Nikolai Zefirov on 13 September, 2005

Nikolai Zefirov was born in Yaroslavl, Russia, on 13th September, 1935. He obtained a M. S. degree in Chemistry from Moscow State University in 1958 and remained there to pursue a Ph. D. degree with Professor Yuriev. He holds a Cand. Sci. (1961) and a D. Sci. degrees (1966) from Moscow State University. From his first appointment as a research chemist, Nikolai Zefirov has worked in Moscow State University for 45 years where he has held various teaching and research appointments in the Department of Chemistry. Following a year (1970-71) at Princeton University as a Visiting Scientist, he was appointed as Head of the Heterocyclic Compounds Laboratory in 1971 and became a full professor of Moscow State University in 1981.

At that stage the work of Zefirov's laboratory enjoyed recognition for research excellence both inside and outside Russia. He was elected a Corresponding Member of the Russian Academy of Sciences in 1981 and a Full Member (Academician) in 1987. These high academic ranks reflect the outstanding contribution Professor Zefirov has made to organic synthesis, reactivity, and theory.

The record of his research output includes *inter alia* synthesis of various polycyclic and cage hydrocarbons such as heteroadamantanes, dihomocubanes, bicyclo[3.3.1]nonanes, tricyclodecanes, which were either unknown before or hard to synthesize. A new class of spiro-condensed cyclopropanes – triangulanes – was discovered and general synthetic methods were

devised for chain, branched, and cyclosubstituted triangulanes. An unprecedented phenomenon of competitive covalent binding of nucleofugal anions in carbocationic processes was opened up, which resulted in (i) dozens of new conjugated addition reactions, (ii) the introduction of many new reagents such as μ-oxodiphenyliodosotriflate (Zefirov reagent), and (iii) the synthesis of new and hard to obtain covalent perchlorates and fluorosulfates. He became interested in the activation of weak electrophiles and SO_3-modified electrophilic addition which resulted in several new synthetic methods. In the course of studying the regioselectivity of electrophilic addition reactions, a new method of increasing effective electrophilicity of weak electrophiles, the "doping addition", was discovered.

His studies in conformational analysis and dynamic stereochemistry are well known and became textbook material. He discovered new conformational effects such as the "hockey sticks" effect, the effect of coordination stabilization of unstable conformations and the effect of boat-like conformations in diheterobicyclononanes. A general equation relating the product ratio with the rate constants for conformationally mobile systems was derived the well known cases of Curtin-Hammett and conformational-equilibria control being the limiting cases. On the basis of a combinatorial approach, algebraic chirality criteria for point 3D configurations and their superpositions were deduced. The general approach to the quantitative description of cyclic molecule conformations based on the functions of torsional angles was suggested and successfully used in numerous stereochemical studies.

Being a Russian Academician, Professor Zefirov was appointed as Director of the Institute of Physiologically Active Compounds of the Russian Academy of Sciences in 1989, retaining at the same time his university positions. In addition, in 1993 he took the Organic Chemistry Chair at Moscow State University. He carries out a colossal research, pedagogical, and organizational job in his three current affiliations: Institute of Physiologically Active Compounds, Moscow State University, and the Zelinsky Institute of Organic Chemistry where he is Head of the Laboratory of Mathematical Chemistry and Computer-Aided Organic Synthesis.

His career has been marked by outstanding academic achievement with more than 900 research papers. His scientific and professional contributions have been recognized by numerous awards and duties. Twice he was awarded the Prize of the Government of Russia for scientific contributions, in 1989 and in 2001. Nikolai Zefirov holds two Russian state orders: Order of Honor (1985) and Order of Friendship of Nations (1995). In 1983, he received the Lomonosov Award from Moscow State University for published works and excellent teaching. In 1994, the Russian Academy of Sciences awarded him the Butlerov Award for outstanding results achieved in dynamic stereochemistry. Zefirov was Head of the Division of Organic Chemistry in the Russian Mendeleev Chemical Society in 1974-1991; currently he is President of the Russian Society for Medicinal Chemistry, a member of the Russian Chemical Society and the American Chemical Society.

Research Interests

The research interests of Nikolai Zefirov have ranged widely over theoretical and synthetic organic chemistry, including such rapidly growing branches as medicinal chemistry and computer-aided molecular design. In fact, Zefirov is a founder of systematic *in silico* medicinal chemistry studies in Russia.

Mathematical chemistry and computer-aided molecular design. Development of advanced methodologies and computer programs for the design of (a) new organic reactions, (b) organic compounds with desirable properties; creation of formal logical approach to organic reactions; development of new molecular descriptors for QSAR, application of artificial neural networks in QSAR/QSPR, development of the molecular field topology analysis method and the solution of inverse problem in QSAR for various descriptors.

Design and synthesis of organic structures, novel organic reagents and reactions. Investigations in the field of competitive binding of nucleofugal anions and new prospective reactions such as deamination, deiodination, nitrosylation, *etc*. Novel reagents in organic chemistry: derivatives of hypervalent iodine, selenium, tellurium, halogeno- and nitrosulfates, sulfofluorides of trivalent iodine, carboxylates of xenon, novel fluorinating reagents and others. Novel types of unique structures such as organic perchlorates, triflates, stable azides, compounds bearing bond C – xenon. Synthetic studies of strained, high-energetic hydrocarbon structures, heterocycles, crown-ethers, and cage compounds.

Medicinal chemistry. A new model of neurodegenerative changes induced by β-amyloid was recently developed in the field of neuroprotector compounds. The construction of 3D models of all glutamate, adenosine, and melatonin receptors resulted in the development of new, highly active neuroprotective agents. Discovery of potent anticancer agents based on using original methods of "structure–biological activity" analysis and unique laboratory cancer models. The prospective anticancer agents under study are some natural lactones, indole-type heterocycles, and some insect toxins as precursors.

Vladimir A. Palyulin
Department of Chemistry,
Moscow State University,
Moscow 119992, Russia

Selected Publications

1. Zefirov, N. S. Stereochemistry of olefine oxymercurization. *Usp. Khim. (Russ. Chem. Rev.)* **1965**, *34 (7)*, 1272.

2. Zefirov, N. S.; Shekhtman, N. M. Effect of coordination stabilization of unstable conformations. *Dokl. Akad. Nauk SSSR (Doklady Chemistry)* **1967**, *177 (4)*, 842.
3. Zefirov, N. S.; Chapovskaya, N.K. Reaction of fumaronitrile with sodium azide. *Zh. Org. Khim. (Russ. J. Org. Chem.)* **1968**, *4 (7)*, 300.
4. Kadzyauskas, P. P.; Zefirov, N. S. Nitrosochlorinations of olefines. *Usp. Khim. (Russ. Chem. Rev.)* **1968**, *37 (7)*, 1243.
5. Zefirov, N. S.; Shekhtman, N. M. Anomeric effect. *Usp. Khim. (Russ. Chem. Rev.)* **1971**, *40 (4)*, 593.
6. Averina, N. V.; Zefirov, N. S. Novel synthesis of 2-oxa-adamantane. *Chem. Commun.* **1973**, *6*, 197.
7. Zefirov, N. S.; Kazimirchick, I. V. Conformational analysis of sulfur-containing six membered heterocycles. *Usp. Khim. (Russ. Chem. Rev.)* **1974**, *43 (2)*, 252.
8. Zefirov, N. S., Conformational analysis of bicyclo[3.3.1]nonanes. *Usp. Khim. (Russ. Chem. Rev.)* **1975**, *44 (3)*, 413.
9. Averina, N. V.; Zefirov, N. S. Advances in heteroadamantane synthesis. *Usp. Khim. (Russ. Chem. Rev.)* **1976**, *45 (6)*, 1077.
10. Zefirov, N. S. The problem of conformational effects. *Tetrahedron* **1977**, *33 (24)*, 3193.
11. Zefirov, N. S. Stereochemical studies. XXI. General equation of relationship between products ratio and conformational equilibrium. *Tetrahedron* **1977**, *33 (20)*, 2719.
12. Zefirov, N. S.; Samoshin, V. V.; Subbotin, O. A.; Baranenkov, V. I.; Wolfe, S. The *gauche* effect. On the nature of the interaction between electronegative substituents in *trans*-1,2-disubstituted cyclohexanes. *Tetrahedron* **1978**, *34 (19)*, 2953.
13. Smit, W. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. Episulfinium ions: myth and reality. *Acc. Chem. Res.* **1979**, *12 (8)*, 282.
14. Zefirov, N. S.; Tratch, S. S. Systematization of tautomeric processes and formal-logical approach to the search for new topological and reaction types of tautomerism. *Chemica Scripta* **1980**, *15 (1)*, 4.
15. Zefirov, N. S.; Makhonkov, D. I. Advances in pernitriles chemistry. *Usp. Khim. (Russ. Chem. Rev.)* **1980**, *49 (4)*, 637.
16. Drozd, V. N.; Zefirov, N. S. Sigmatropic additions and cyclosubstitutions in five-membered heterocyclic compounds containing exocyclic double bond. *Sulfur Reports* **1981**, *1 (5)*, 271.
17. Minkin, V. I.; Zefirov, N. S.; Korobov, M. S; Averina, N. V.; Boganov, A. M.; Nivorozhkin, L. E. 1,3,5-Trimethyl derivative of square pyramidal cation $(CH)_5^+$. *Zh. Org. Khim. (Russ. J. Org. Chem.)* **1981**, *17 (12)*, 2616.
18. Zefirov, N. S.; Mahonkov, D. I. X-philic reactions. *Chem. Rev.* **1982**, *82 (6)*, 615.
19. Zefirov, N. S.; Koz'min, A. S.; Zhdankin, V. V.; Kirin, V. N.; Yur'eva, N. M.; Sorokin, V. D. Competitive binding of super-weak nucleophiles in carbocationic-like processes. *Chemica Scripta* 1983, *22 (4)*, 195.

20. Zefirov, N. S., Koz'min, A. S. *Salt effects in electrophilic addition (Ad_E) reactions as a new principle of synthesis. Soviet Scientific Reviews. B. Chemistry,* Harwood Academic Publishers GmbH: Amsterdam; 1985; Vol. 7, pp 297-339.
21. Zefirov, N. S.; Zyk, N. V.; Kolbasenko, S. I.; Kutateladze, A. G. Sulfur trioxide assisted electrophilic addition of R_2NCl to olefins. *J. Org. Chem.* **1985**, *50 (23)*, 4539.
22. Zefirov, N. S.; Koz'min, A. S. Competitive binding of nucleofugal anions in carbocationic-like processes. *Acc. Chem. Res.* **1985**, *18 (5)*, 154.
23. Zefirov, N. S. SO_3-assisted electrophilic addition. *Organic synthesis: modern trends. Materials of 6-th IUPAC Symposium*. Blackwell, Oxford: UK, 1986; pp 129-138.
24. Zefirov, N. S. Approach to systematization and design of organic reactions. *Acc. Chem. Res.* **1987**, *20 (7)*, 237.
25. Zefirov, N. S.; Zhdankin, V. V.; Koz'min, A. S. Synthesis and properties of covalent organic perchlorates. *Usp. Khim. (Russ. Chem. Rev.)* **1988**, *57 (11)*, 1815.
26. Stankevich, I. V.; Stankevich, M. I.; Zefirov, N. S. Topological indices in organic chemistry. *Usp. Khim. (Russ. Chem. Rev.)* **1988**, *57 (3)*, 337.
27. Trushkov, I. V.; Zhdankin, V. V.; Koz'min, A. S.; Zefirov, N. S. Cubic reaction coordinate diagram in the nucleophilic substitution process. *Tetrahedron Lett.* **1990**, *31 (22)*, 3199.
28. Zefirov, N. S.; Tratch, S. S. Symbolic equations and their applications to reaction design. *Analytica Chim. Acta* **1990**, *235 (1)*, 115.
29. Zefirov, N. S.; Kozhushkov, S. I.; Kuznetsova, T. S.; Kokoreva, O. V.; Lukin, K. A.; Ugrak, B. I.; Tratch, S. S. Triangulanes: stereoisomerism and general method of synthesis. *J. Am. Chem. Soc.* **1990**, *112 (21)*, 7702.
30. Zefirov, N. S.; Surmina, L. S; Sadovaya, N. K.; Blochin, A. V.; Tyurehodjaeva, M. A.; Bubnov, Yu. N.; Lavrinovich, L. I.; Ignatenko, A. V.; Grishin, Yu. K.; Zelenkina, O. A.; Kolotyrkina, N. G.; Kudrevich, S. V.; Koz'min, A. S. Reactions of [1.1.1]propellane. *Zh. Org. Khim. (Russ. J. Org. Chem.)* **1990**, *26 (11)*, 2317.
31. Zefirov, N. S.; Palyulin, V. A. Conformational analysis of bicyclo[3.3.1]nonanes and their hetero analogs *In Topics in Stereochemistry;* Eliel, E. L.; Wilen, S. H., Eds, John Wiley & Sons Inc.: NY, 1991; Vol. 20, pp 171-230.
32. Zhdankin, V. V.; Tykwinski, R.; Williamson, B. L; Stang, P. J.; Zefirov, N. S. (Dicyanoiodo)benzene - a stable tricoordinate iodine(III) compound with three carbon ligands. *Tetrahedron Lett.* **1991**, *32 (6)*, 733.
33. Kutateladze, A. G.; Zefirov, N, S.; Zyk, N. V. Reactions of sulfenic and sulfoxylic acid derivatives with olefins in the presence of sulfur trioxide and its complexes. *Sulfur Reports* **1992**, *11 (2)*, 233.
34. Stang, P. J.; Zhdankin, V. V.; Tykwinski, R.; Zefirov, N. S. (Dicyano)iodonium triflate - novel iodonium species and a versatile reagent for the preparation of iodonium salts via an iodonium transfer reaction with organostannanes *Tetrahedron Lett.* **1992**, *33 (11)*, 1419.
35. de Meijere, A.; Kozhushkov, S. I.; Spaeth, T.; Zefirov, N. S. A new general approach to bicyclopropylidene. *J. Org. Chem.* **1993**, *58 (2)*, 502.

36. Zefirov, N. S.; Zyk, N. V.; Beloglazkina, E. K.; Kutateladze, A. G. Thiosulfonates: synthesis, reactions and practical applications *Sulfur Reports* **1993**, *14*, 223.
37. Kartashov, V. R.; Skorobogatov, E. V.; Zefirov, N. S. Reactions of cyclopropene compounds with electrophilic reagents *Usp. Khim. (Russ. Chem. Rev.)* **1993**, *62 (10)*, 991.
38. Zyk, N.V.; Denisko, O. V.; Zefirov, N. S. Vinylic esters of sulfonic and sulfur acids *Zh. Org. Khim. (Russ. J. Org. Chem.)* **1994**, *30 (3)*, 461.
39. Lukin, K. A., Zefirov, N. S. Spiroannulated cyclopropanes. *Chemistry of cyclopropyl group,* Rappoport, Zvi, Ed; 1995, Wiley: UK, Vol. 2, pp 861-885.
40. Zefirov, N. S.; Kuznetzova, T. S; Zefirov, A. N. Triangulanes. *Izv. Akad. Nauk, Ser. Khim. (Russ. Chem. Bull.)* **1995**, *9*, 1613.
41. Zyk, N. V.; Beloglazkina, E. K.; Zefirov, N. S. Sulfur trioxide: reagent, acid, catalyst *Zh. Org. Khim. (Russ. J. Org. Chem.)* **1995**, *31 (9)*, 1283.
42. Trushkov, I, V.; Chuvylkin, N. D.; Koz'min, A. S; Zefirov, N. S. Correlation methods in analysis and prediction of reactivity in processes of nucleophilic substitution *Izv. Akad. Nauk, Ser. Khim. (Russ. Chem. Bull.)* **1995**, *5*, 804.
43. Zefirov, N. S. Novel reagents of iodine(+3) and sulfur. *Pure Applied Chem.* **1996**, *68,* (4), 881.
44. Kasumov, T. M.; Koz'min, A. S; Zefirov, N. S..Chemistry of inorganic sulfonates and sulfates of polyvalent iodine. *Usp. Khim. (Russ. Chem. Rev.)* **1997**, *66 (10)*, 936.
45. Kuznetzova, T. S; Eremenko, O. V.; Kokoreva, O. V.; Averina, E. B.; Zefirov, A. N.; Zefirov, N. S. New studies on triangulanes. *Zh. Org. Khim. (Russ. J. Org. Chem.)* **1997**, *33 (6)*, 916.
46. Brel, V. K., Zefirov, N. S. Hypervalent compounds of xenon. In *"Chemistry of hypervalent compounds",* Kin-ya Akiba, Ed.; Wiley-VCH: New York, 1999; Ch. 13, pp 389-408.
47. Pirkuliev, N. S.; Brel, V. K.; Zefirov, N. S. Alkenyliodonium salts. *Usp. Khim.* **2000**, *69 (2)*, 118.
48. Bachurin, S. O.; Tkachenko, S. E.; Baskin, I. I.; Lermontova, N. N.; Mukhina, T. V.; Petrova, L; Ustinov, A.; Proshin, A.; Grigor'ev, V. V.; Lukoyanov, N. V.; Palyulin, V. A.; Zefirov, N. S. Neuroprotective and cognition enhancing properties of MK-801 flexible analogs. Structure-activity relationships. *Annals N. Y. Acad. Sci* **2001**, *939*, 219.
49. Averina, N. V.; Borisova, G. S; Zefirov, N. S. Advances in chemistry of 4-azatricyclo[4.3.1.1^{3,8}]undecane (4-azahomoadamantane) derivatives. *Zh. Org. Khim. (Russ. J. Org. Chem.)* **2001**, *37 (7)*, 959.
50. Zefirova, O. N.; Zefirov, N. S. Biologically active compounds interacting with serotonin (5-hydroxytriptamine) receptors. *Usp. Khim. (Russ. Chem. Rev.)* **2001**, *70 (4)*, 382.
51. Leontiev, A. V.; Fomicheva, O. A.; Proskurnina, M. V.; Zefirov, N. S. Contemporary chemistry of nitrogen oxide (I). *Usp. Khim. (Russ. Chem. Rev.)* **2001**, *70 (2)*, 107.
52. Ivanov, A. A.; Baskin, I. I.; Palyulin, V. A.; Baraldi, P. G.; Zefirov, N. S. Molecular modelling of the human A2b adenosine receptor and an analysis of the binding modes of its selective ligands *Mendeleev Commun.* **2002**, 211.

53. Zefirov, N. S.; Palyulin, V. A. Fragmental Approach in QSPR. *J. Chem. Inf. Comput. Sci.* **2002**, *41 (5)*, 1112.
54. Zefirov, N. S.; Tratch, S. S.; Molchanova, M. S. The ARGENT program system: a second-generation tool aimed at combinatorial search for new types of organic reactions. 1. Main concepts and potentialities. *Commun. Math. Chem.* (*MATCH*) **2002**, *46*, 253.
55. Budynina, E. M.; Ivanova, O. A.; Averina, E. B.; Grishin, Yu. K.; Kuznetzova, T. S; Zefirov, N. S. Bromotrinitromethane in three-component reactions with olefines. *Dokl. Akad. Nauk. (Doklady Chemistry)* **2002**, *387 (2)*, 200.
56. Ivanov, A. A.; Baskin, I. I.; Palyulin, V. A.; Zefirov, N. S. Molecular modeling of adenosine receptors. *Vestn. Mosk. Univ., Ser. Khim. (Moscow Univ. Bull., Chemistry Series)* **2002**, *43 (4)*, 231.
57. Baskin, I. I.; Tikhonova, I. G.; Palyulin, V. A.; Zefirov, N. S. Selectivity Fields: Comparative Molecular Field Analysis (CoMFA) of the Glycine NMDA and AMPA Receptors. *J. Med. Chem.* **2003**, *46*, 4063.
58. Matveeva, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G.; Zefirov, N. S. A novel catalytic three-component synthesis (Kabachnick-Fields reaction) of α-amino-phosphonates from ketones. *SYNLETT* **2003**, *15*, 2321.
59. Tikhonova, I. G.; Baskin, I.I.; Palyulin, V. A.; Zefirov, N. S. CoMFA and homology-based models of the glycine binding site of N-methyl-D-aspartate receptor. *J. Med. Chem.* **2003**, *46 (9)*, 1609.
60. Halberstam, N. M.; Baskin, I. I.; Palyulin, V. A.; Zefirov, N. S. Neural networks as a method for searching "structure–property" relationships for organic compounds. *Usp. Khim. (Russ. Chem. Rev.)* **2003**, *72 (7)*, 706.