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Professor Nikolay S. Zefirov

Full member of Russ. Acad. Sci.
Distinguished Professor of MSU.
Full member of International Academy of Mathematical Chemistry.

Chair of Organic Chemistry,
Chairman.
Department of Chemistry of
Moscow State Lomonosov
University (MSU)

Scientific Leader,
Institute of Physiologically
Active Compounds (IPhAC)
Russ.Acad.Sci.
Chernogolovka

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MSU
Chem. Dept.

IPhAC
RAS

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Department of Chemistry of Moscow State Lomonosov University (MSU)

1935, Yaroslavl

1953

1961
Ph.D.

1966
Dr.habil.

Corresponding member of RAS 1981

Full member of RAS 1987

Director of IPhC RAS 1989

Scientific Leader,
Institute of Physiologically Active Compounds (IPhAC) Russ.Acad.Sci. Chernogolovka

“I was born, fed with nipple, grew, lived, work, grew older…
Life will pass by as Azore islands just passed.” ***Vl. Mayakovskii***

? 2010

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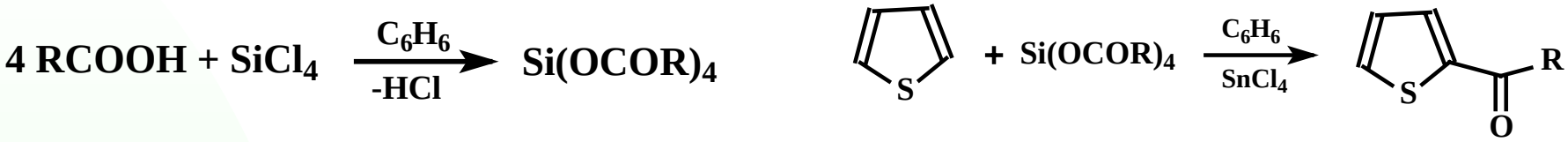
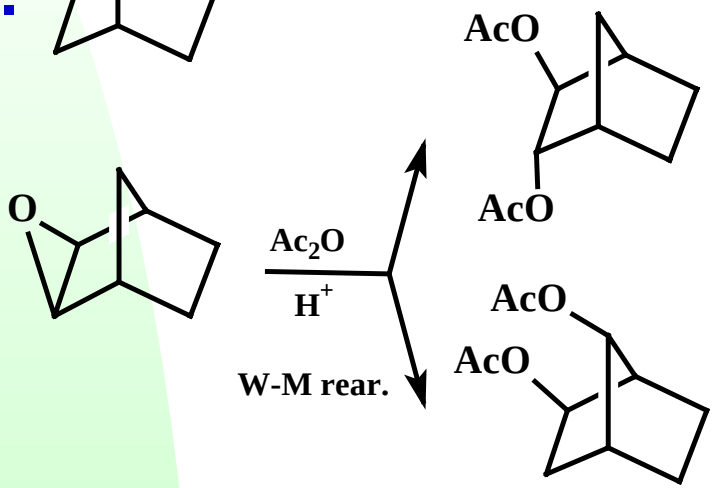
IPhAC RAS

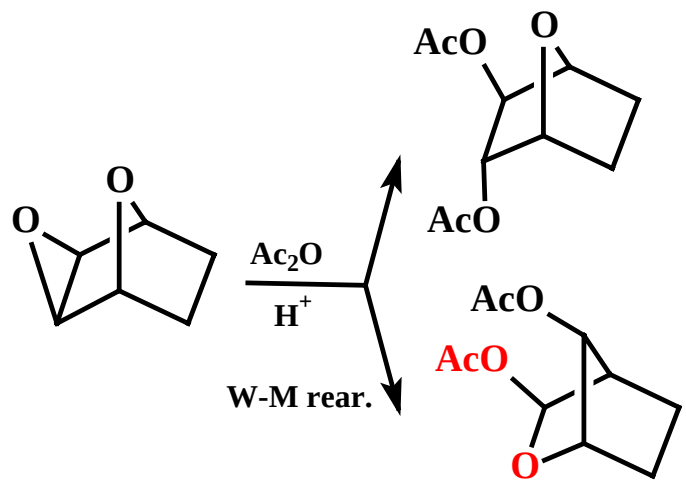
Chemical childhood and maturation

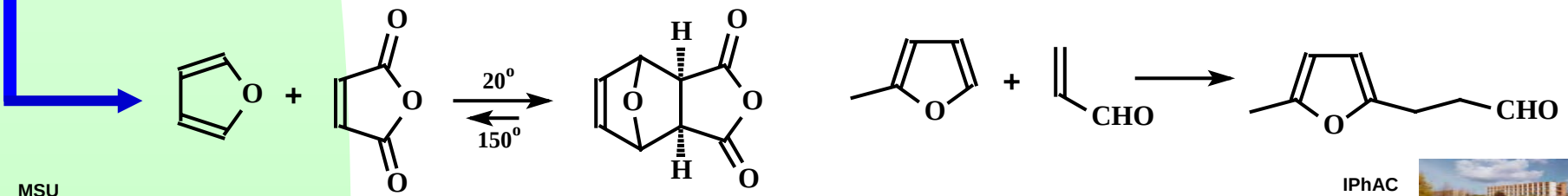
Yu.K.Yur'ev, G.B.Elyakov, N.S.Zefirov, *Zh.Obshch.Khim.*, 26, 3341 (1956); *Ibid*, 27, 3264 (1957);



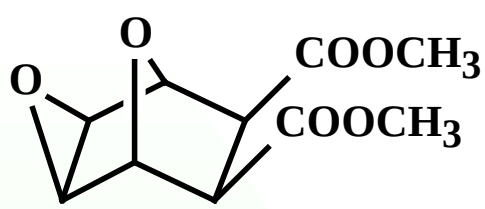
chemistry without NMR!

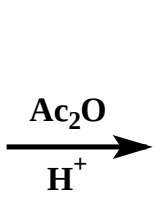


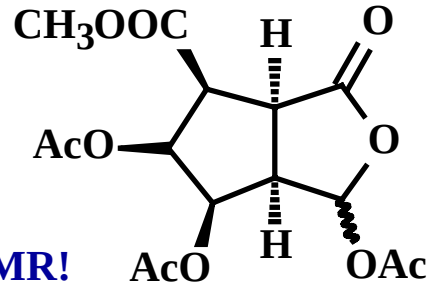


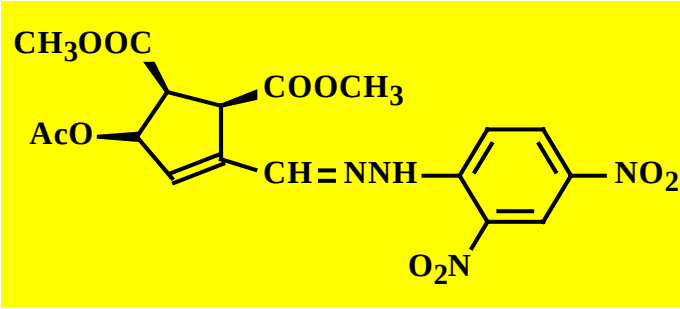


Chemical childhood and maturation (2)

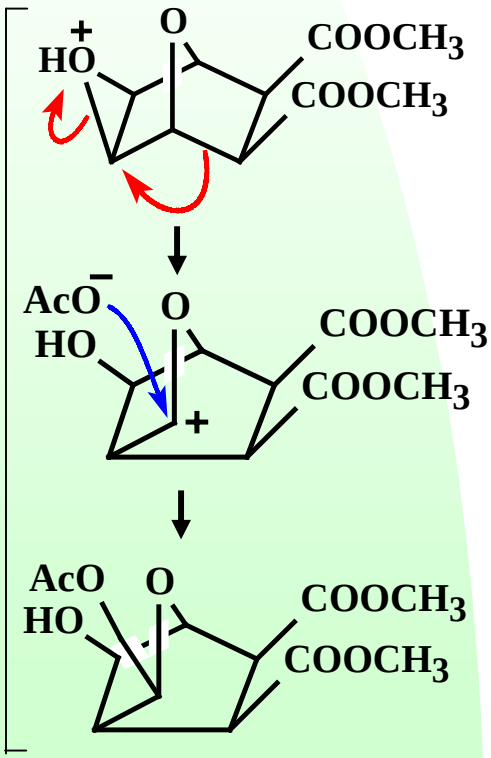


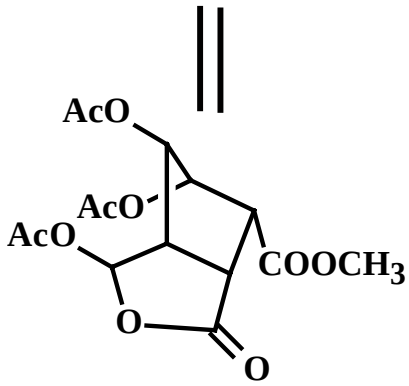


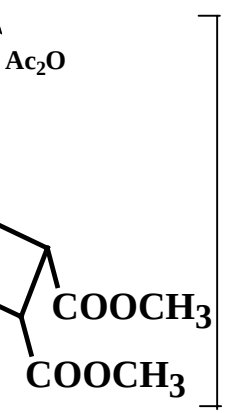




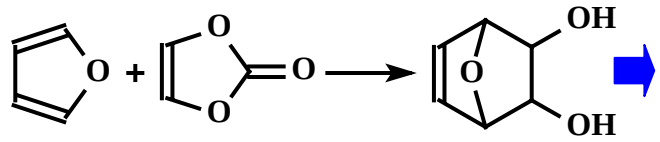
chemistry without NMR!



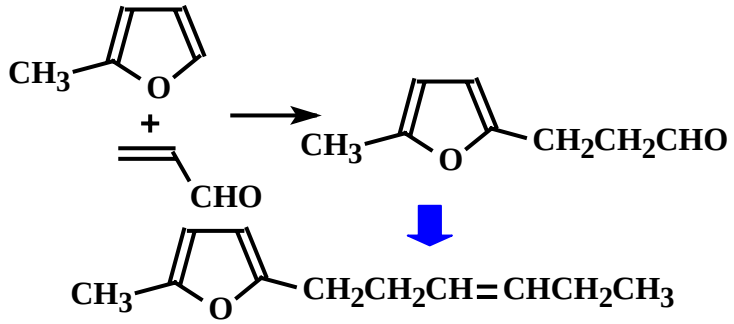


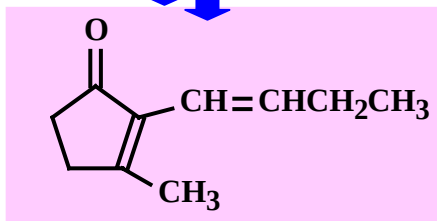


Pathway to cyclitols



Synthesis of trans-jasmone





Yu.K.Yur'ev, N.S.Zefirov, 1961 – 1963; N.S.Zefirov, 1963 – 1966;

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- **Synthetic organic chemistry**
- **Physical organic chemistry, MO**
- **Stereochemistry and conformational analysis**
- **Mathematical chemistry and computer science**
- **Medicinal chemistry**

MSU Chem. Dept.

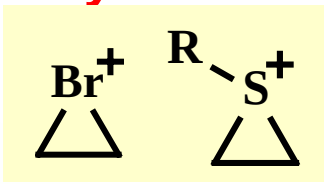
Appr. 1500 patents and papers in referred journals

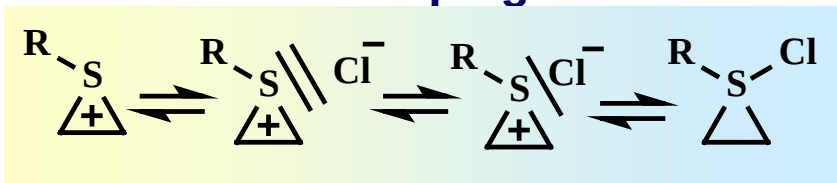
IPhAC RAS

Synthetic organic chemistry

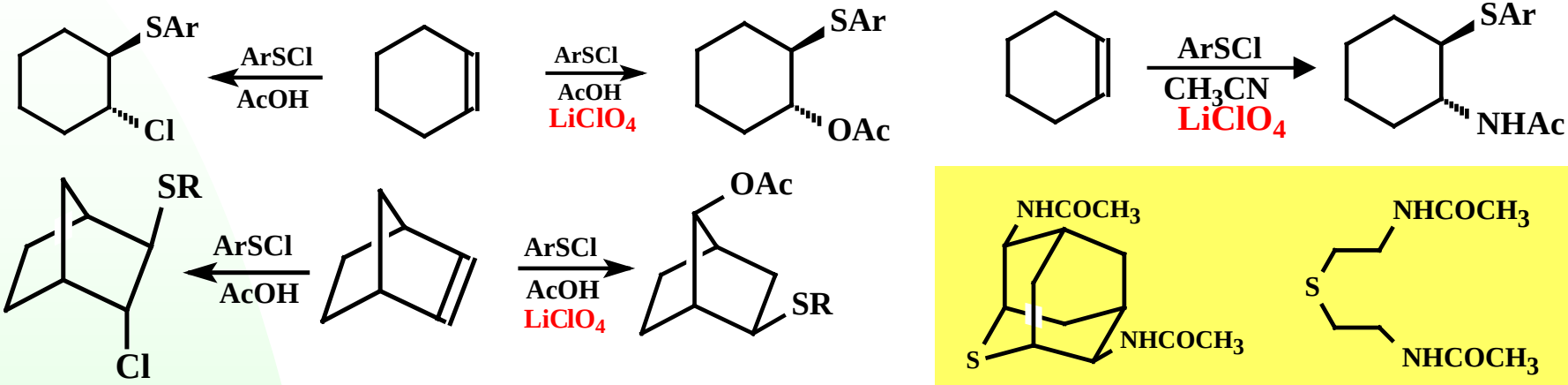
- Novel approaches in Ad_E reactions: (a) “doping-addition”, (b) SO_3-mediated addition.
- Nucleophilic properties of nucleofugic anions. Synthesis of organic perchlorates, triflates, fluorosulfates etc.
- Novel reactions and reagents. Novel hypervalent I^{+3}, Xe^{+2}, Se^{+4}, Te^{+4} reagents.
- Cage compounds: (a) heteroadamantanes, (b) bicyclo-[3.3.1]nonanes, (c) skeletal rearrangements.
- Cyclopropanes, triangulanes and related polycyclic compounds. High energy compounds.
- Polynitrocompounds. Synthesis using $C(NO_2)_4$.
- Synthesis of heterocyclic compounds of different types.
- Photochemical reactions: (a) synthesis with hexachlorocyclopentadiene, synthesis of λ^5-phosphinolines from phosphonium-iodonium ylides.

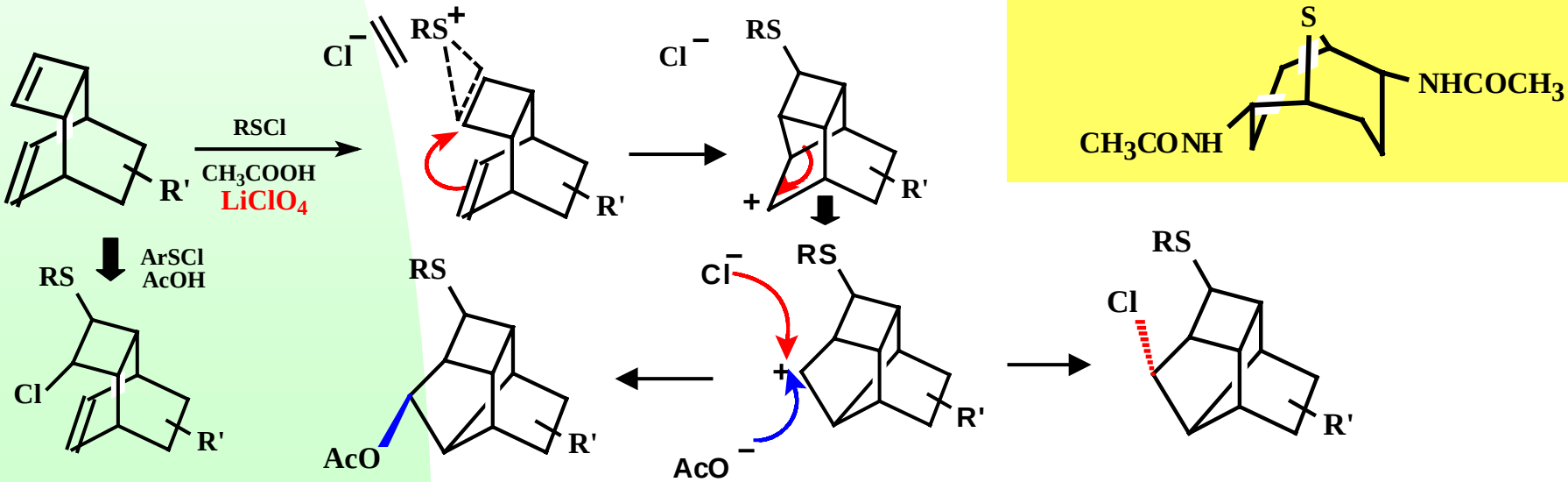
Synthetic organic chemistry: ion-pair mechanism of Ad_E-reactions and "doping-addition".





Thioamidation reaction





N.S.Zefirov, et al., *Tetr.*, 1975, *31*, 2948; 1979, *35*, 2759; 1985, *41*, 5219; *Tetr. Lett.*, 1979, 3533; *Acc.Chem.Res.*, 1979, *12*, 282; *J.Org.Chem.*, 1981, *46*, 5264; 1982, *47*, 1471

Synthetic organic chemistry: nucleophilic properties of nucleofugal anions.

General scheme of nucleophilic substitution: $R-X \xrightarrow{Y^-} R-Y$, $R-X \xrightarrow{Z^-} R-Z$; $R-Y / R-Z = ?$

TfO^- ClO_4^- FSO_3^- $ClSO_3^-$ H_2O — F^- AcO^- Cl^- Br^- I^- OH^- CN^- N_3^-

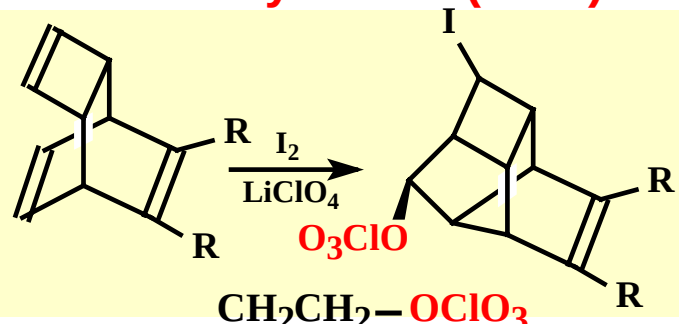
nucleofug ⟷ nucleophile

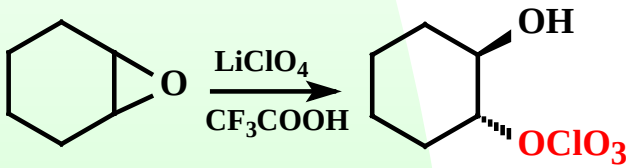
The competitive covalent binding of "nucleofugal" anions is a general phenomenon for a variety of carbocationic-like reactions.

Discovery № 293 (1984)

$H_2C(OSO_2CF_3)-CH_2Cl \xleftarrow[LiOSO_2CF_3]{Cl_2} H_2C=CH_2 \xrightarrow[LiOSO_2F]{Cl_2} H_2C(OSO_2F)-CH_2Cl$

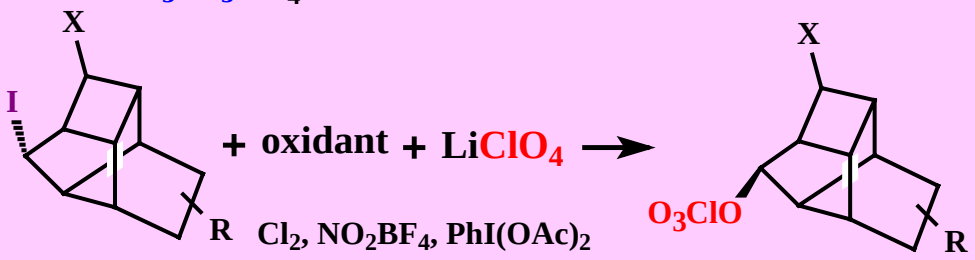
$CH_2=CH_2 + NO_2BF_4 + LiClO_4 \longrightarrow O_2N-CH_2CH_2-OClO_3$

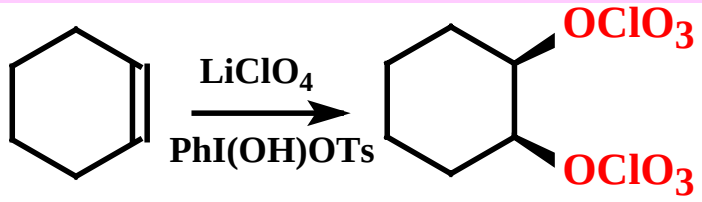




$H_2C(O)CH_2 + NO_2BF_4 + LiClO_4 \longrightarrow CH_2(O_2NO)CH_2-OClO_3$

$CH_3I \xrightarrow[CF_3SO_3^-Bu_4N^+]{Cl_2} CH_3OSO_2CF_3$ $\quad CH_2I_2 + LiClO_4 + NO_2BF_4 \longrightarrow O_3ClO-CH_2-OClO_3$





State Award, USSR (1989)

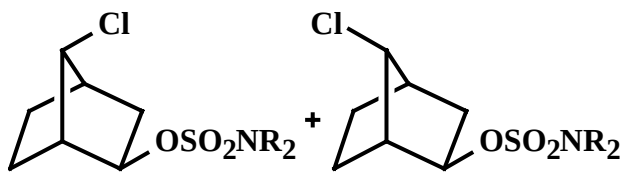
N.S.Zefirov et al., *Chem.Scripta*, 1983, *22*, 195; *J.Org.Chem.*, 1985, *50*, 1872; *Acc.Chem. Res.*, 1985, *18*, 154; *Usp.Khim*, 1988, *57*, 1815.

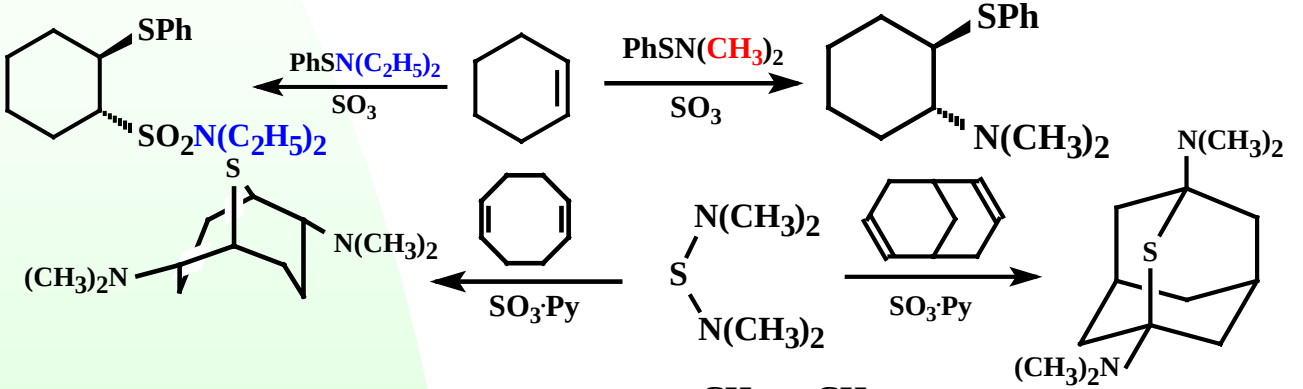
Synthetic organic chemistry: SO_3-mediated Ad_E-reactions.(POX_3)

FSO_3^- $ClSO_3^-$

$$\overset{\delta+}{X}-\overset{\delta-}{Y} + SO_3 \rightarrow X-SO_3Y \rightleftharpoons X^+ + {}^-SO_3Y$$

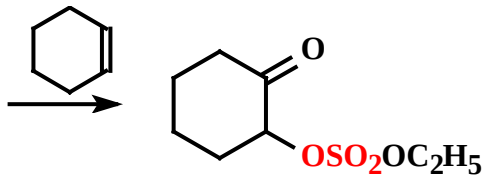
$R_2N-Cl + SO_3 \rightarrow [R_2NSO_2O-Cl]$





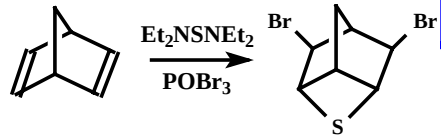
$Cl-Cl + SO_3 \rightarrow [ClOSO_2Cl] \xrightarrow{CH_2=CH_2} ClCH_2CH_2OSO_2Cl$

$C_2H_5O-NO + SO_3 \rightarrow [C_2H_5OSO_2-ONO]$



XeF_2 $\xrightarrow{SO_3}$ $[FSO_2O-XeF]$ $\xrightarrow{Cl_2C=CCl_2}$ $FSO_2OCCl_2-CCl_2F$

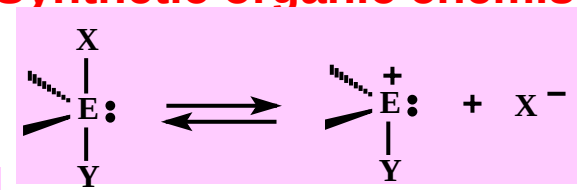
XeF_2 $\xrightarrow{2\ SO_3}$ $[FSO_2O-Xe-OSO_2F]$ $\xrightarrow{ClFC=CFCl}$ $FSO_2OCFClCFClOSO_2F$



R_2N-Cl	R_2NSO_2OCl
RO-Cl	$ROSO_2OCl$
Cl-Cl	$ClSO_2OCl$
RS-Cl	$RSOSO_2Cl$
O_2NOR	O_2NOSO_2OR
ON-OR	$ONOSO_2OR$
RS-NR_2	$RSOSO_2NR_2$
R_2NSNR_2	$S(OSO_2NR_2)$
RS-SR’	$RSOSO_2SR’$
RS-OR’	$RSOSO_2OR’$
RSe-OR’	$RSeOSO_2OR’$
RSe-NR_2	$RSeOSO_2NR_2$
F-Xe-F	$FXeOSO_2F$
	$FO_2SO_2XeOSO_2OR$
RCO-F	$RCOOSO_2F$

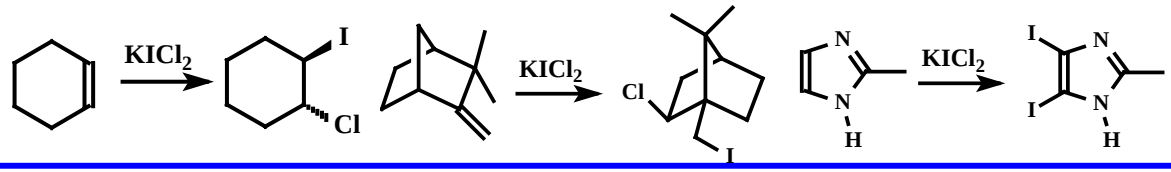
N.S.Zefirov et al., *J.Org.Chem.*,1984,*49*, 4086; *Pure.Appl.Chem.*, 1996, *68*, 881; N.S.Zefirov, N. V. Zyk et al., *J.Org.Chem.*,1985,*50*, 4539; N.V.Zyk, E.K.Beloglazkina, N.S.Zefirov, *ЖОрХ*,1995,*31*, 1283;

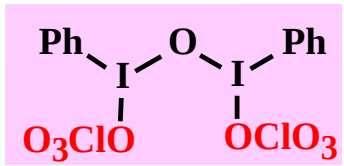
Synthetic organic chemistry: novel hypervalent reagents I^{+3}, Xe^{+2}, Se^{+4}, Te^{+4}.

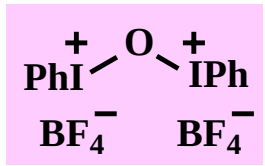


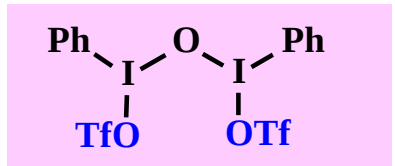
$KICl_2$

$CH_2{=}CH_2 \xrightarrow{KICl_2} ClCH_2CH_2I$

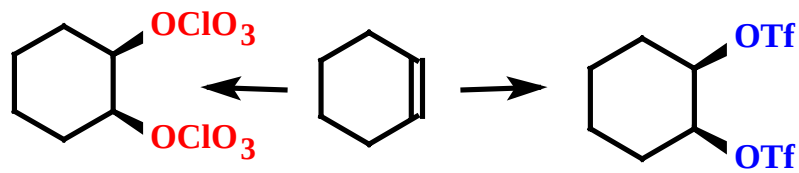






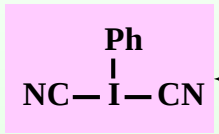


Zefirov's reagent

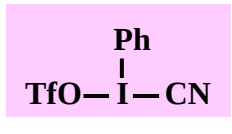


Tetr.Lett., 1986, 3971; *Synlett.*, 1993, 193; *Angew. Chem.,Int.Ed.Engl.*, 1992, *31*, 274;

J. Org. Chem., 1992, *57*, 6496; *Tetr.*, 1992, 7149 *J.Org.Chem.*,1999, 64, 1630;

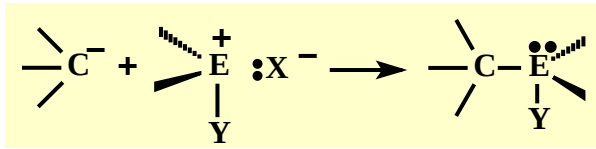


$\xleftarrow{2\ Me_3SiCN}$ $PhI{=}O$ $\xrightarrow[Me_3SiOTf]{Me_3SiCN}$



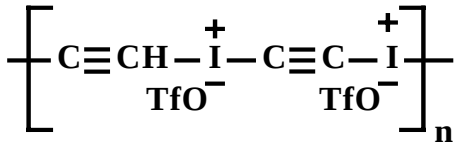
$O{=}I{-}OSO_2CF_3$

$O{=}I{-}OSO_2F$

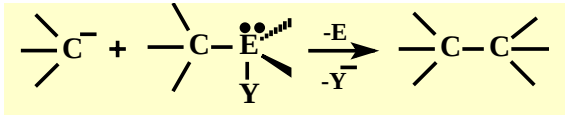


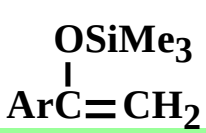
$2\ RC{\equiv}CSiMe_3 \xrightarrow{O{=}I{-}OSO_2CF_3} RC{\equiv}C{-}\overset{+}{I}{-}C{\equiv}CR\ TfO^-$

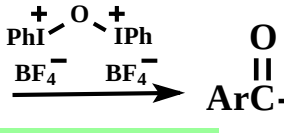
$R_3SnC{\equiv}CSnR_3 \xrightarrow{O{=}I{-}OSO_2CF_3}$

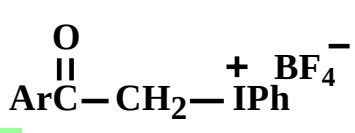


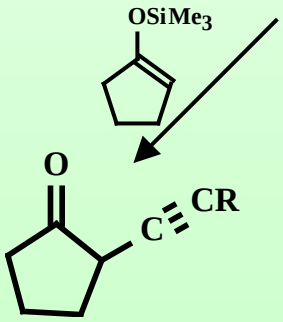
$RC{\equiv}CH \longrightarrow RC{\equiv}C{-}\overset{+}{I}Ph\ X^-$







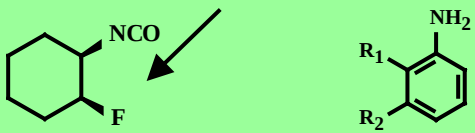


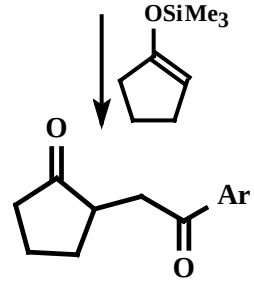


$RC{\equiv}CLi \xrightarrow[-LiBF_4]{BF_3} RC{\equiv}CBF_2 \xrightarrow{XeF_2} RC{\equiv}C{-}\overset{+}{Xe}\ BF_4^-$

^{128}Xe NMR : δ -1898 ppm from XeF_2

$FXeNCO \xleftarrow{Me_3SiN{=}C{=}O} XeF_2 \xrightarrow[TfOH]{Me_3SiN{=}C{=}O} TfOXeNCO$





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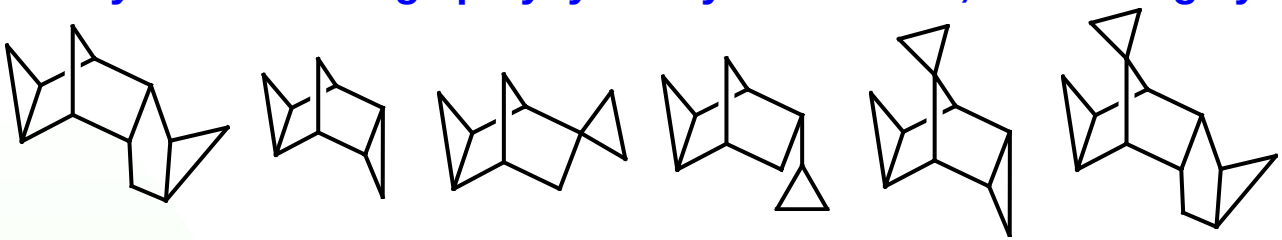
N.S Zefirov, V.V Zhdankin, P.Stang, R. Caple, V.K. Brel, S.A. Lermontov, et. al.,

IPhAC RAS

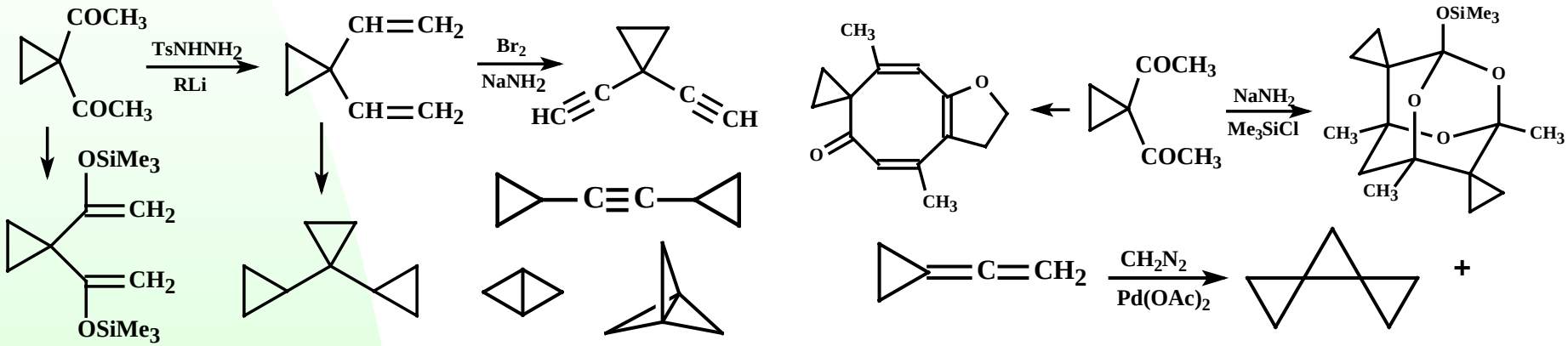
Synthetic organic chemistry: cyclopropanes

Synthesis of cage/polycyclic hydrocarbons, containing cyclopropane fragments

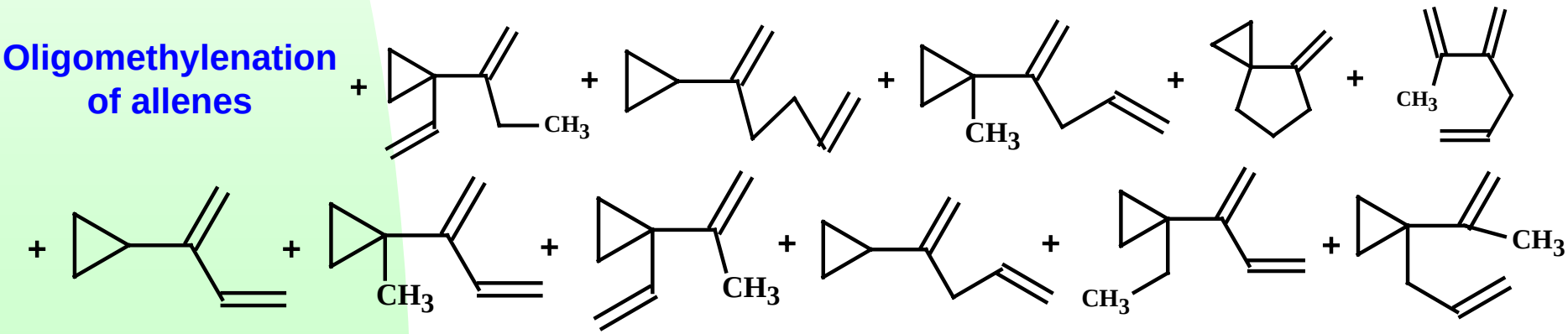


High density :
up to > 1 g/cm^3

N.S.Zefirov, K.A.Lukin,I.V.Kazimirchik,G.F.Bebich et al., *Zhur.Org.Chem.*, 1983, *19*, 105, 253; 1984, *20*, 1221,1691;



Oligomethylenation of allenes



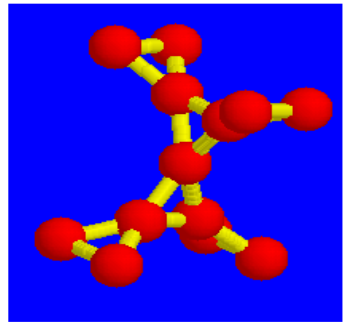
MSU Chem. Dept.

N.S.Zefirov, T.S.Kuznetsova, S.Kozhushkov, K.A.Lukin et al., *Zhur.Org.Chem.*, 1987, *23*, 2548; 1988, *24*, 673,1644,1648; *Tetrah.*, 1982, *38*, 1693; 1986, *42*, 709; *Chem.Ber.*, 1991, *124*, 371;

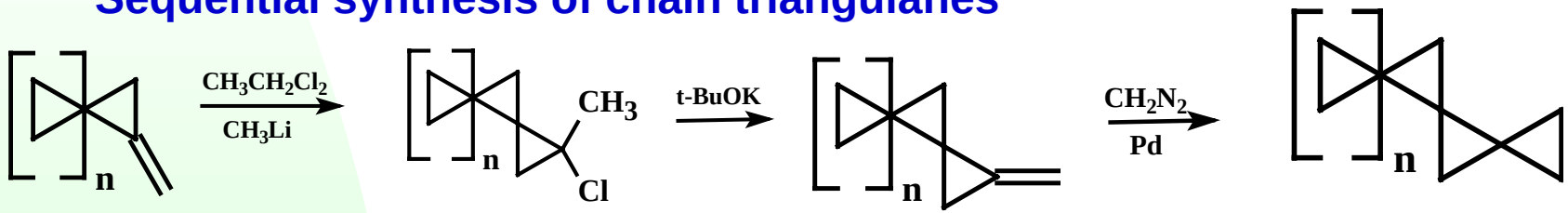
IPhAC RAS

Synthetic organic chemistry: triangulanes

- **triangulanes are the class of hydrocarbons whose skeleton is constructed from *spiro-attached* cyclopropane units.**
- **triangulanes have a large diversity of structures and complex steroisomerism.**
- **triangulanes possess unusual physical (*e.g. strain*) and chemical properties**

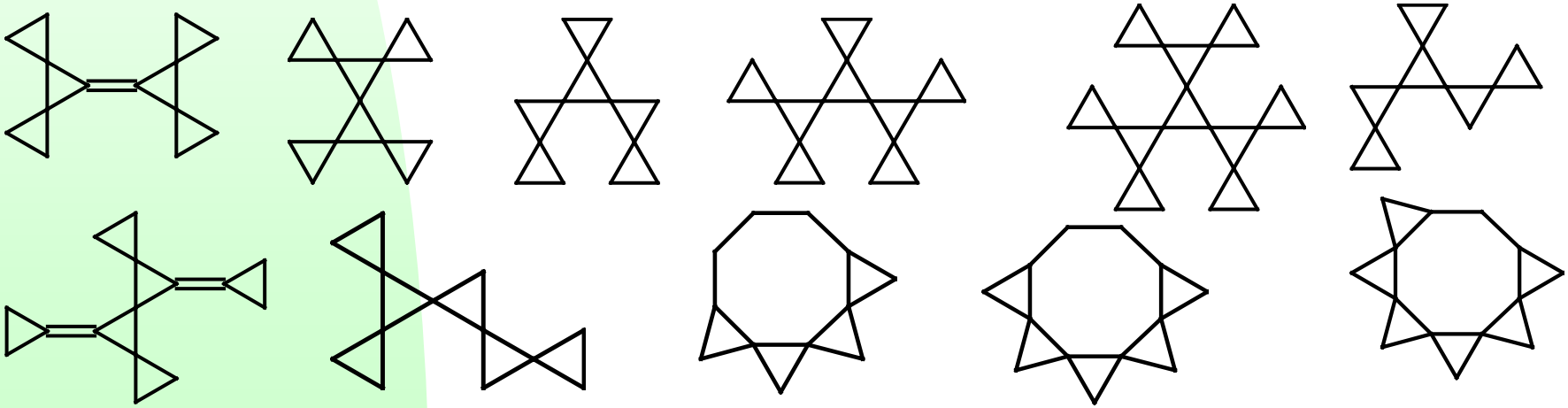


Sequential synthesis of chain triangulanes



First step **: Homologization of methylenecyclopropane unit**

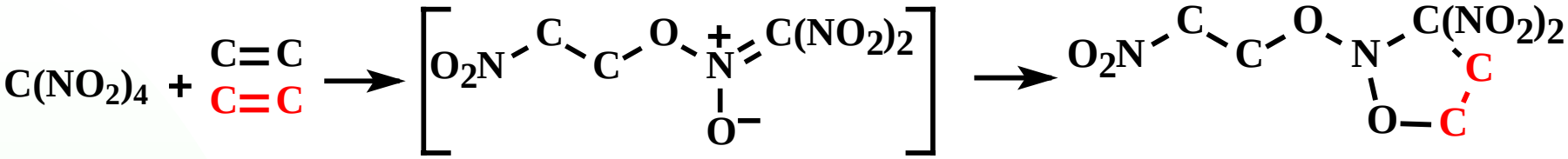
Second step**: Termination by cyclopropanation**



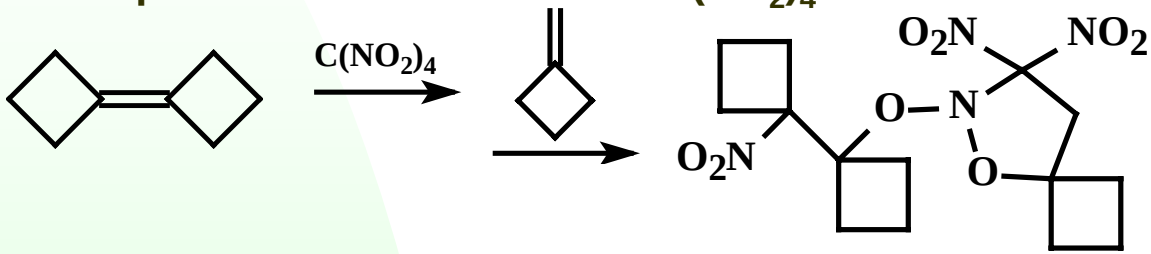
N.S.Zefirov, T.S.Kuznetsova et al., *J.Am.Chem.*Soc., 1990, *112*, 7702; *J.Org.Chem.*, 1993, *58*, 502; *J.Org.Chem.*, 1994, *59*, 4087; *Russ.Chem.Bull.*, 1995, 1613; *Zhur.Org.Khim.*, 2000, *36*,228;

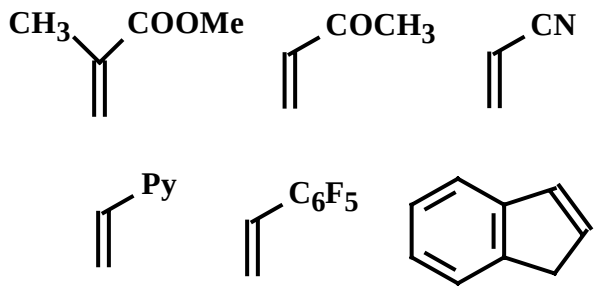
Synthetic organic chemistry: syntheses using $C(NO_2)_4$

General scheme of olefins reaction with $C(NO_2)_4$:

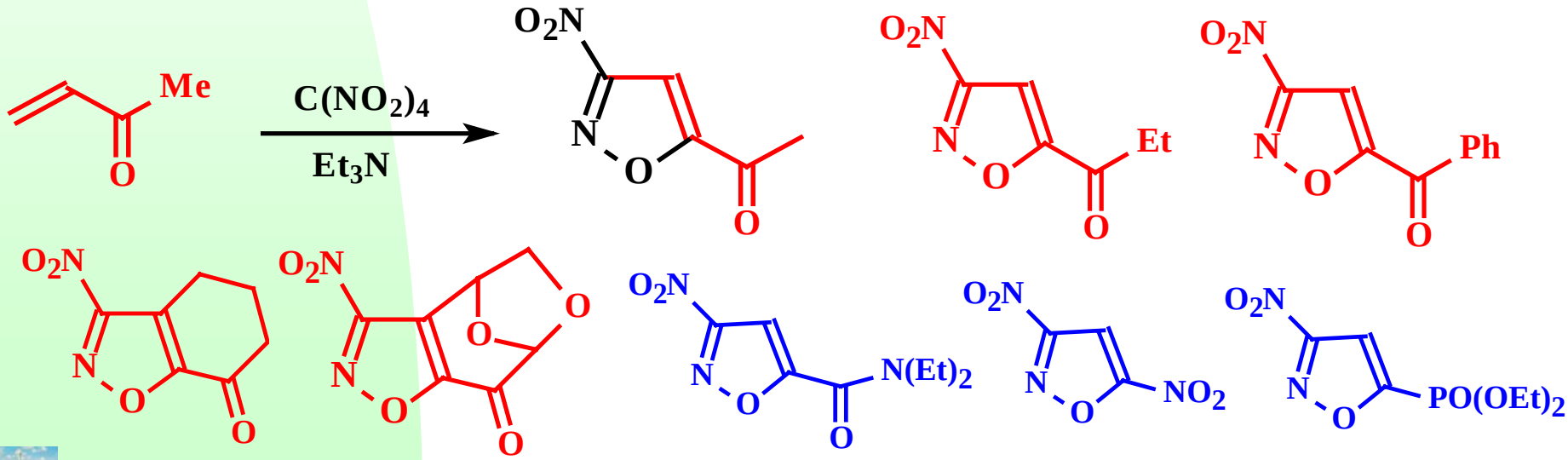


Stepwise tandem reaction of $C(NO_2)_4$ with different olefins





Unusual reaction of α,β-unsaturated ketones with $C(NO_2)_4 \cdot Et_3N$ reagent: $[Et_3\overset{+}{N}\text{-}NO_2][\overset{-}{C}(NO_2)_3]$



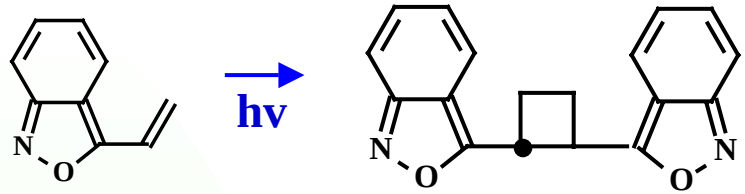
MSU Chem. Dept.

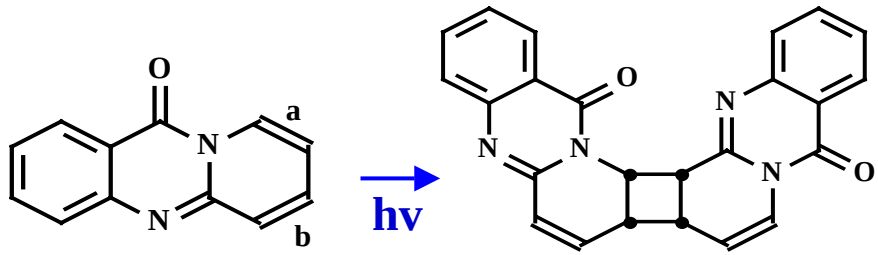
E.B.Averina, T.S.Kuznetzova, N.S.Zefirov, *SYNLETT*, 2009, 1543

IPhAC RAS

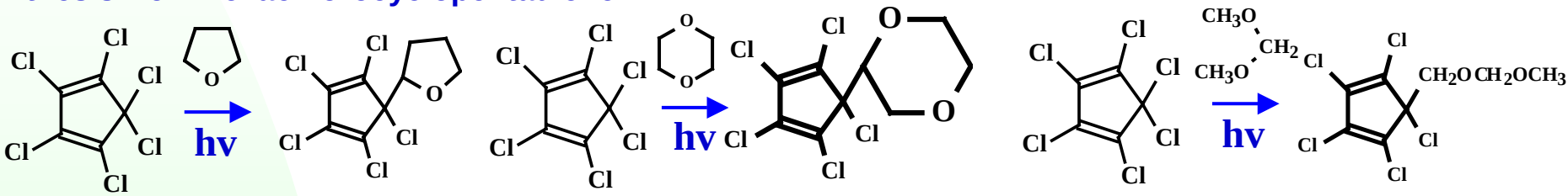
Synthetic organic chemistry: photochemical reactions

[2+2]-Cycloadditions

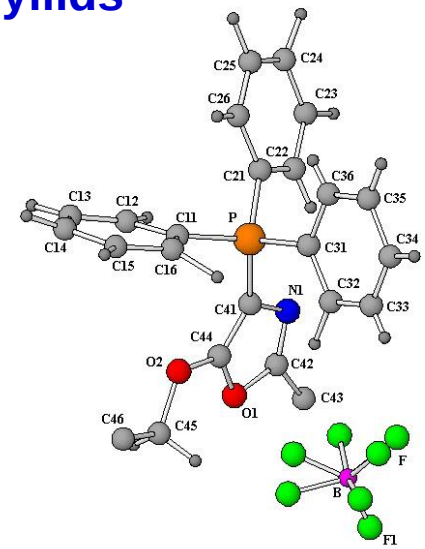


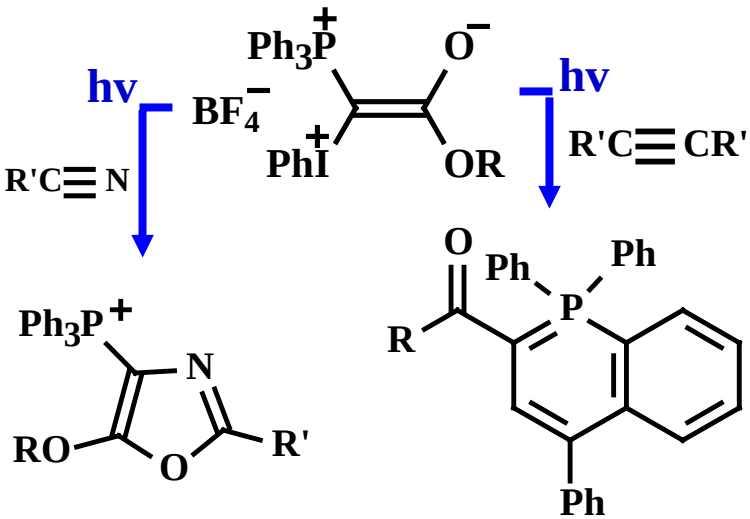


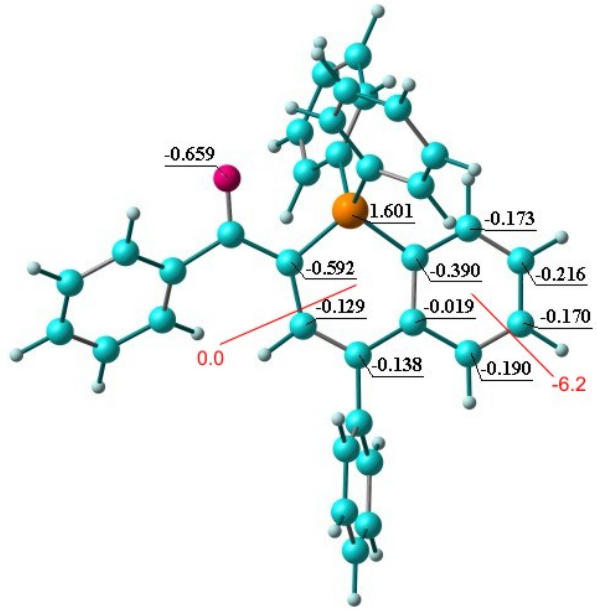
Synthesis from hexachlorocyclopentadiene



Synthesis of oxazoles and λ⁵-phosphinolines from phosphonium-iodonium yilids



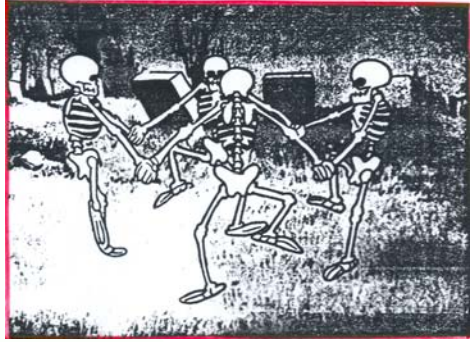




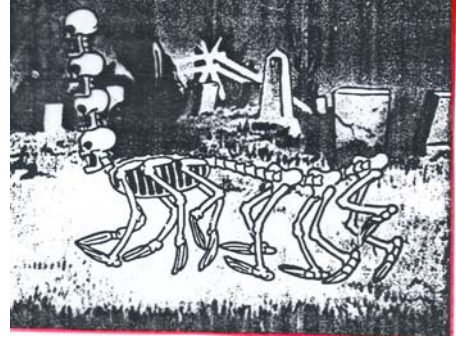
N.S. Zefirov, E.D.Matveeva, R. Gleiter,et. al., *Eur. J. Org. Chem.*, 2009, 2323; N.S. Zefirov, E. D. Matveeva, R. Gleiter,et. al., *J. Org. Chem.*, 2009, *74*, 9428

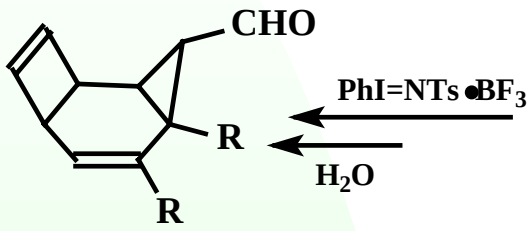
Physical organic chemistry, MO

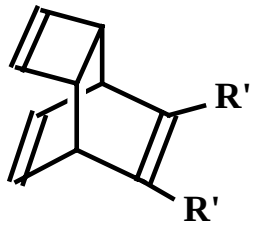
- Kinetics and mechanism of several Ad_E reactions (*e.g.* hydroxymercuration, sulfenylation, nitrosochlorination etc). Skeletal rearrangements in Ad_E reactions.
- Mechanism and skeletal rearrangement in carbenoid transformations.
- MO prediction of novel structural types.
- Calculation of atomic charges – schemes based on redistribution of atomic electronegativities ("Zefirov's charges": Zefirov N.S., et. al., *Dokl. Akad.Sci. USSR.*,1987, *296*, 883; 1989, *304*, 887. Новая зарядная схема: Oliferenko A.A., Palyulin V.V., Zefirov N.S., *J.Phys. Org. Chem.*, 2001, *14*, 355 ; *SAR,QSAR Env. Res.*, 2002, *13*, 297, *Adv. Quntum Chem*., 2006, *51*, 139.).

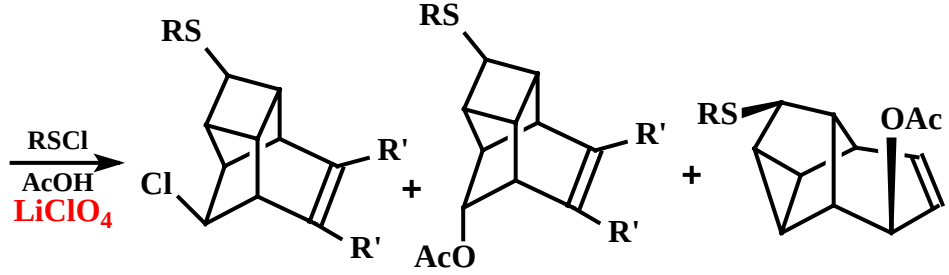


Physical organic chemistry: skeletal rearrangement.

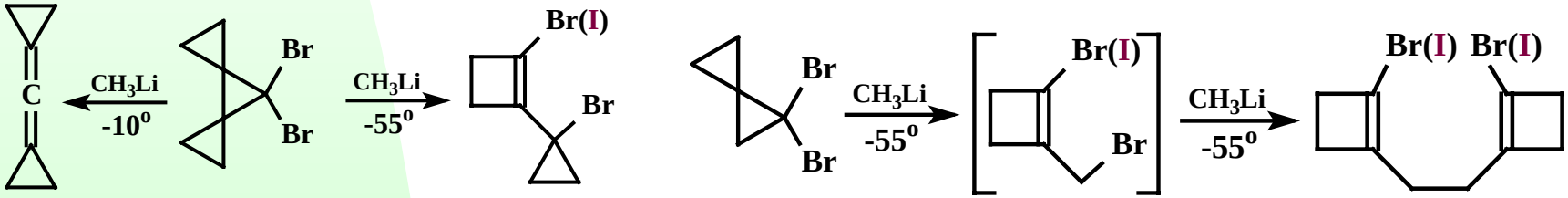


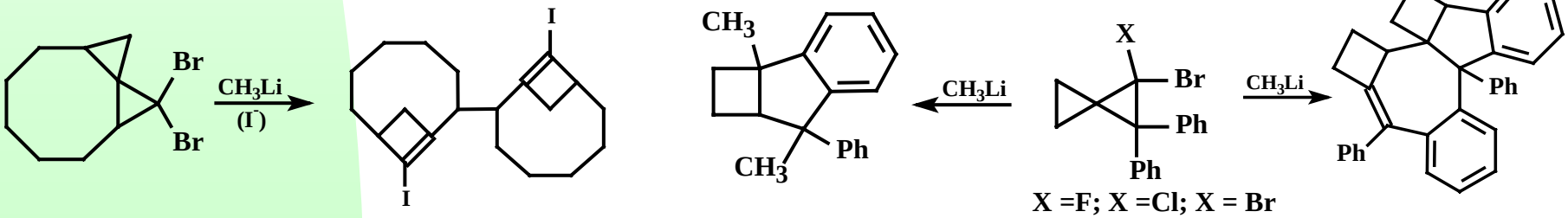






Carbenoid dihalotriangulane rearrangement – mechanistic mystery.





X =F; X =Cl; X = Br

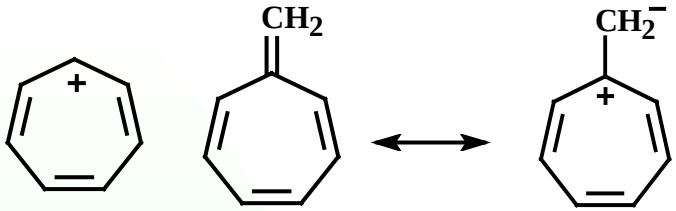
N.S.Zefirov, T.S.Kuznetsova, K.A. Lukin, E.A.Averina et al., *Tetr. Lett.*, 1992, *48*, 9977; *Tetr.*, 2006, *62*, 8814; *Tetr.*, 2009, *65*, 5693;

Physical organic chemistry, MO

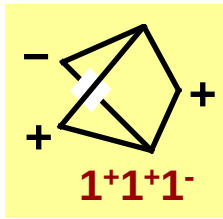
MO prediction of structures of novel types.

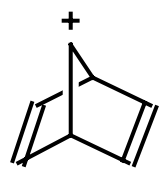
Definition of different types of conjugation

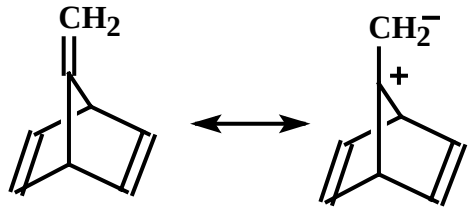
M. Goldstein, R. Hoffmann, *J. A. C. S.*, 1971, *93*, 6193



Pericyclic conjugation



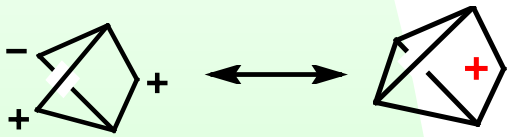




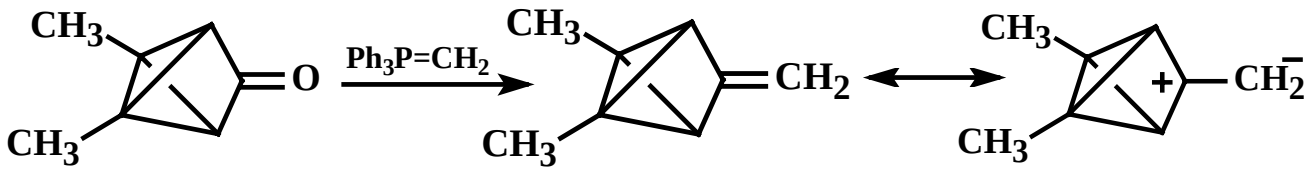
Longicyclic conjugation

W. Stohrer, R. Hoffmann, *J. Am. Chem. Soc.*, 1972, *94*, 1661

Longicyclic conjugation in methylenehomotetrahedrane

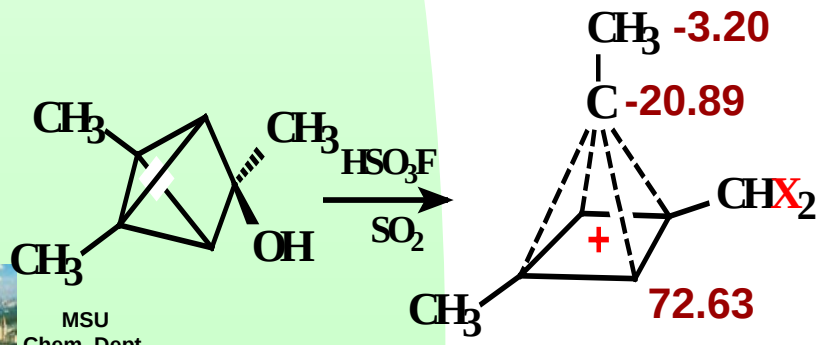


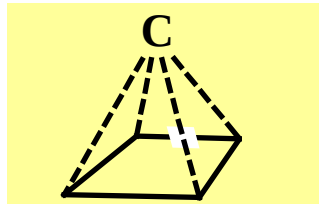
N.S. Zefirov, R. Hoffmann, V.I. Minkin,et. al., *Zh. Org. Khim.*, 1980, *16*, 241



Tri-Me-C_5H_2 pyramidal cation

V.I. Minkin, N.S. Zefirov, et. al., *Zh. Org. Khim.*, 1981, *17*, 2616



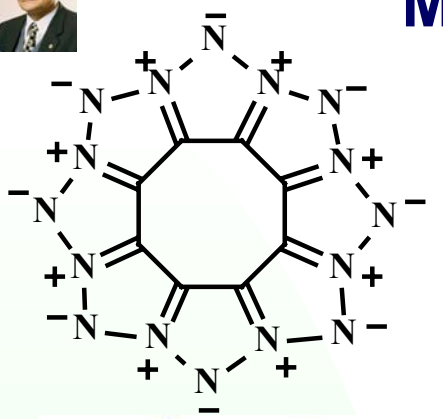


Pyramidane

Physical organic chemistry, MO

MO prediction of structures of novel types.

C_8N_{16}

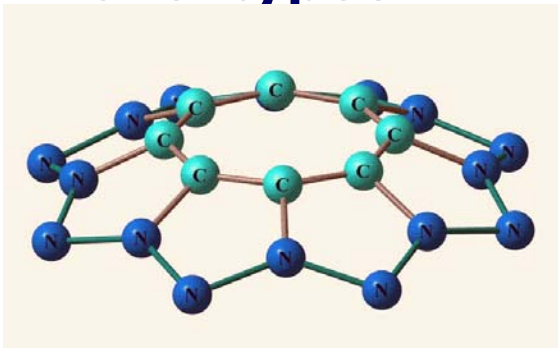


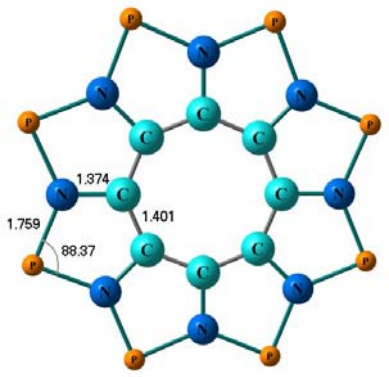
DFT B3LYP/6-311G* data:

bowl shaped, planar C8 ring, C_{8v},

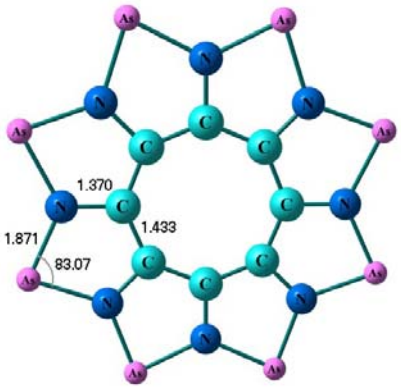
bowl ⇄ bowl >150 kcal/mol

NICS(0) index in the centers of 8- membered ring – 3.3

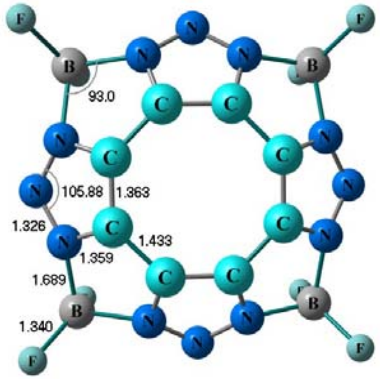




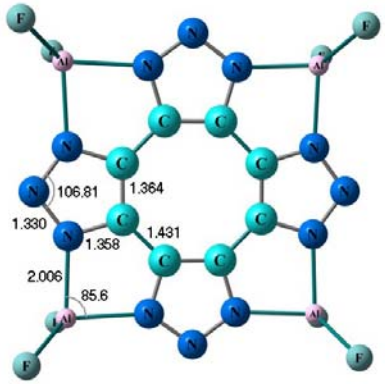
P



As



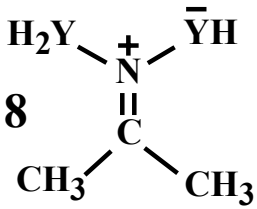
BF_2



AlF_2

Homodesmotic reaction:

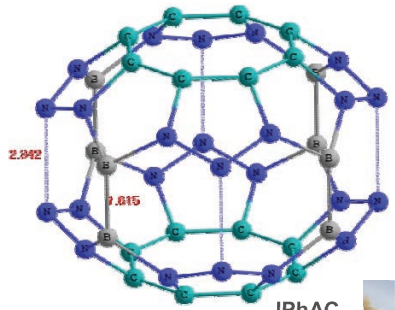
$C_8N_8Y_8 + 8\ YH_3 + 8\ CH_3\text{-}CH_3 \leftrightarrow 8$



ΔE_{arom} : Y = N 87.2 kcal/mol;

Y = P 268.9 kcal/mol; Y = As 246.4 kcal/mol

Stacking-derivatives



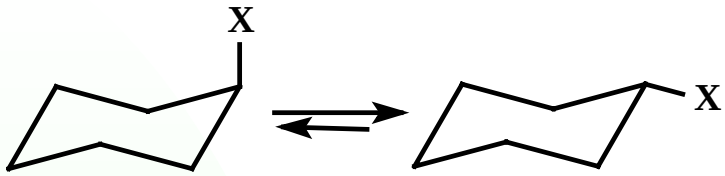
T.Gribanova, N.S.Zefirov, V.I.Minkin, *Dokl. Chem.*, 2009, *426*, 105; *Pure & Appl. Chem.*, 2010, *82*, 1011.

Stereochemistry and conformational analysis.

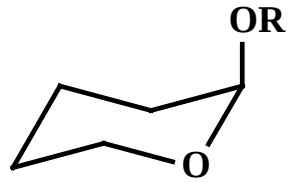
- Stereochemistry of some basic electrophilic additions (*e.g.* oxymercurations, sulfenylations, nitrosochlorination etc).
- The problem of conformational effects. Anomeric effect. "Gauche" and "Hockey-sticks" effects. Search for novel conformational effects and abnormalities (*e.g.* in bicyclo[3.3.1]-nonanes).
- Description of ring shape and puckering. Computer algorithms, programs, and complexes to solve stereochemical problems.
- Reactivity of conformationally mobile systems.
- Conformationally regulated crowns.
- Abstract configurations and chirality - algebraic approach.

Stereochemistry and conformational analysis: the problem of conformational effects.

Conformational analysis: Hassel, Barton (1969); E. Eliel



A = - ΔG_{eq} F, OR, Cl, Br , NR_2, CH_3, $C(CH_3)_3$

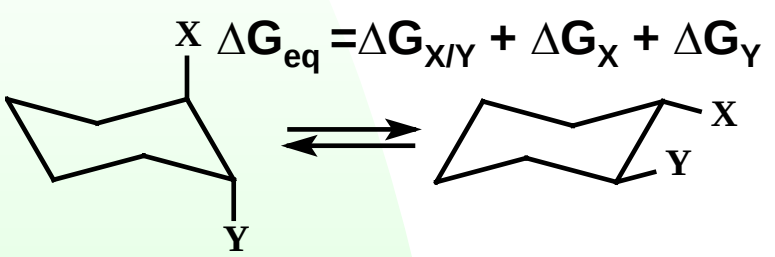


Anomeric effect

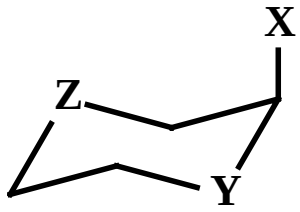
"Rabbit-ears" effect

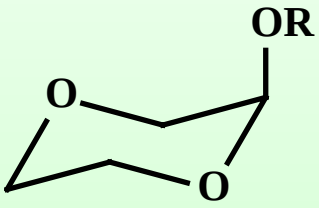
"Gauche-effect"

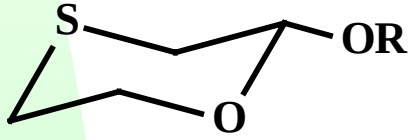
"Δ^2-instability factor"

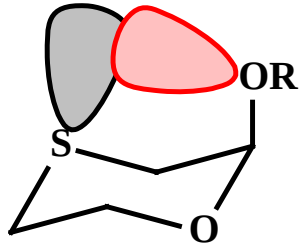


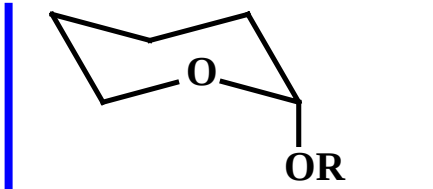
$\Delta G_{eq} = \Delta G_{X/Y} + \Delta G_X + \Delta G_Y$

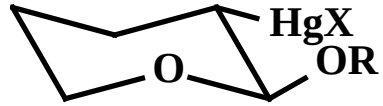


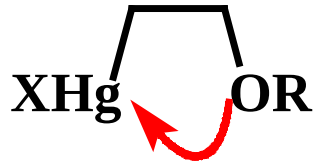


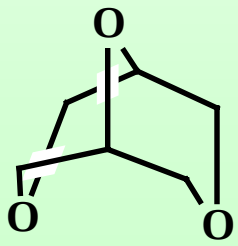


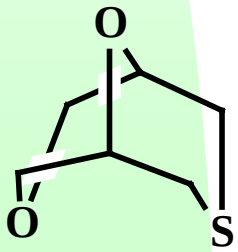


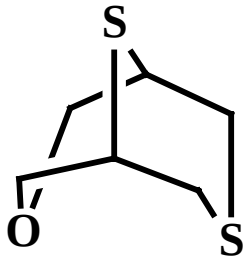


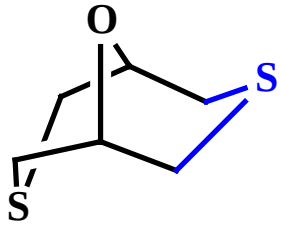


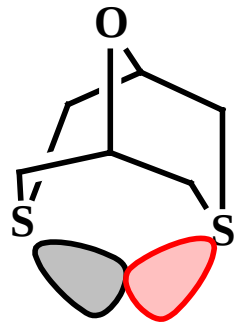










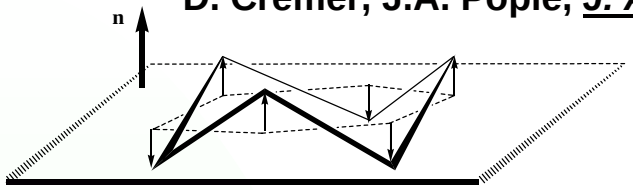


"Hockey-sticks" effect

N.S. Zefirov et. al., *Usp.Khim.*, 1973, *42*, 423; 1975, 44, 413; *Tetr.*, 1976, *32*, 1211;
N.S. Zefirov, V.A. Palyulin, *Topics in Stereochemistry.*, 1994, *34*, 994.

Stereochemistry and conformational analysis: description of ring shape and puckering coordinates.

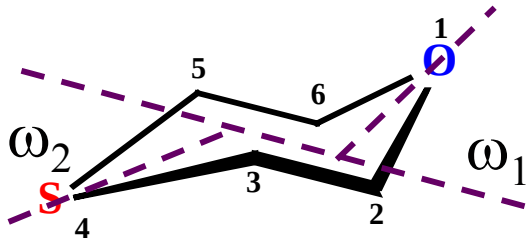
D. Cremer, J.A. Pople, *J. Am. Chem. Soc.*, 1975, *97*, 1354

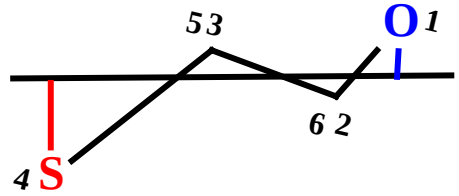


Cremer-Pople method:

(1) Two puckering amplitudes q_2 and q_3

(2) Phase angle φ_2



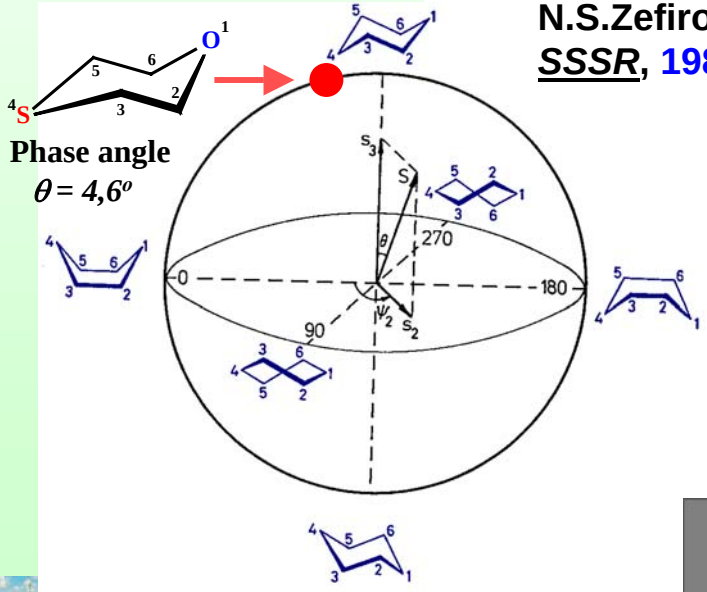


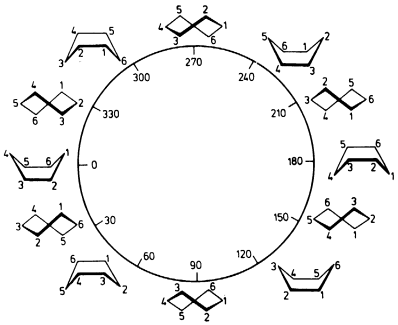
$\omega_2 = 47^o$ $\omega_1 = 56^o$ $C_3S_4C_5$ - flattened

Cremer-Pople method: $C_6O_1C_2$ - flattened

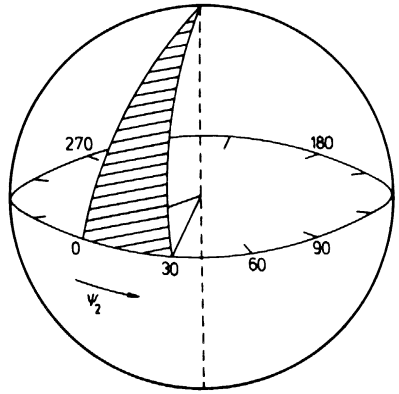
Zefirov-Palyulin method for calculation of puckering coordinates (Sin φ/2)

N.S.Zefirov, V.A.Palyulin, et. al., *Dokl. AN SSSR*, 1980, *252*, 111; *Dokl. AN SSSR*, 1987, *292*, 1380; *J.Phys.Org.Chem.*, 1990, 3, 147.





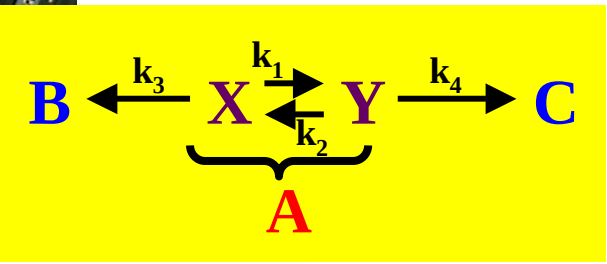
Cut of sphere on equator



Sphere in puckering coordinates.

Minimal narrow sector of change of puckering parameters due to re-enumeration and choice of enantiomer.

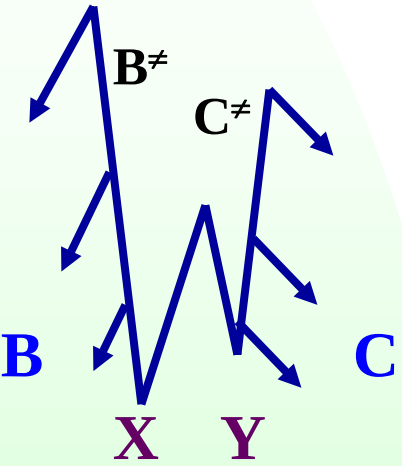
Stereochemistry and conformational analysis: conformation and reactivity.



$K_{eq} = k_1/k_2 = [Y]_0/[X]_0$ $\quad P_\infty = [C]_\infty/[B]_\infty$?

1. Case 1: $k_4, k_3 >> k_1, k_2$ (Curtin-Hammett)

$$P_\infty = [C]_\infty/[B]_\infty = e^{(G_{B\neq} - G_{C\neq})/RT} = K_{eq} \bullet k_4/k_3$$



Curtin-Hammett principle:

"relative amount of products…are completely independent of the relative population of the conformers and depend only on the difference in free energy of the transition states…"

2. Case 2: conformational control (kinetic quenching): $k_4, k_3 << k_1, k_2$

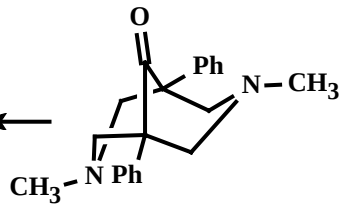
$$P_\infty = K_{eq}$$

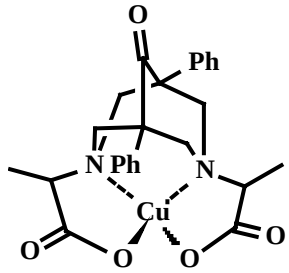
3. General case: any value for k_4, k_3, k_2, k_1 :

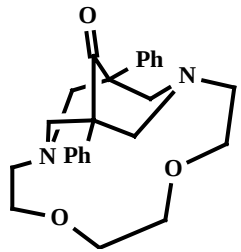
$$P_\infty = [C]_\infty/[B]_\infty = K_{eq} \bullet k_4(k_1+k_2+k_3)/k_3(k_1+k_2+k_4)$$

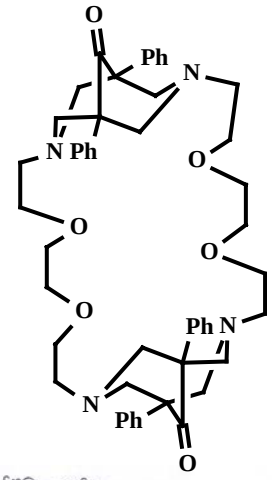
N.S.Zefirov, *Tetrahedron*, 1977, *33*, 2719; *Zh. Org. Chem.*, 1979, *15*, 1098;
J. Seeman, *Chem.Rev.*, 1983, *83*, 83.

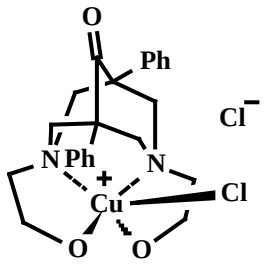
Stereochemistry and conformational analysis:
crowns and complexation

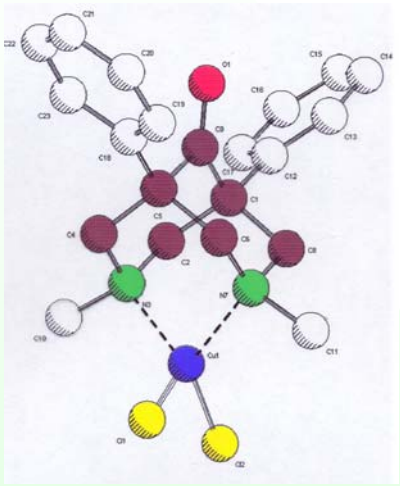


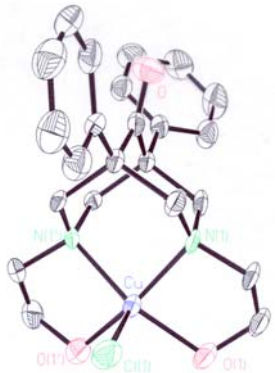


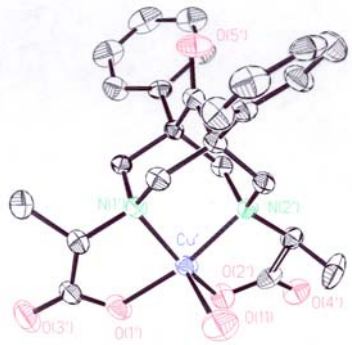


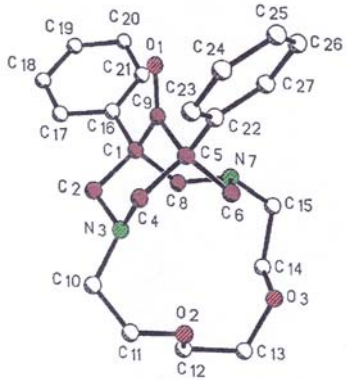


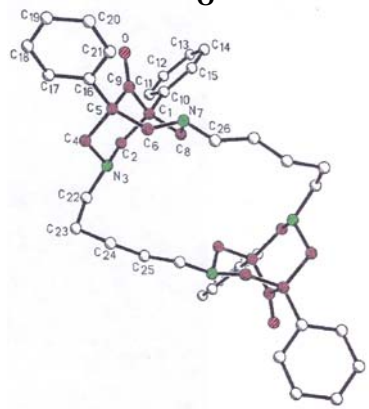




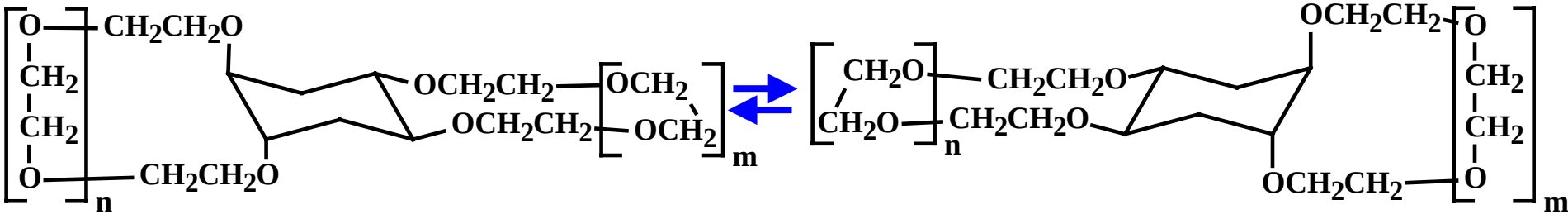






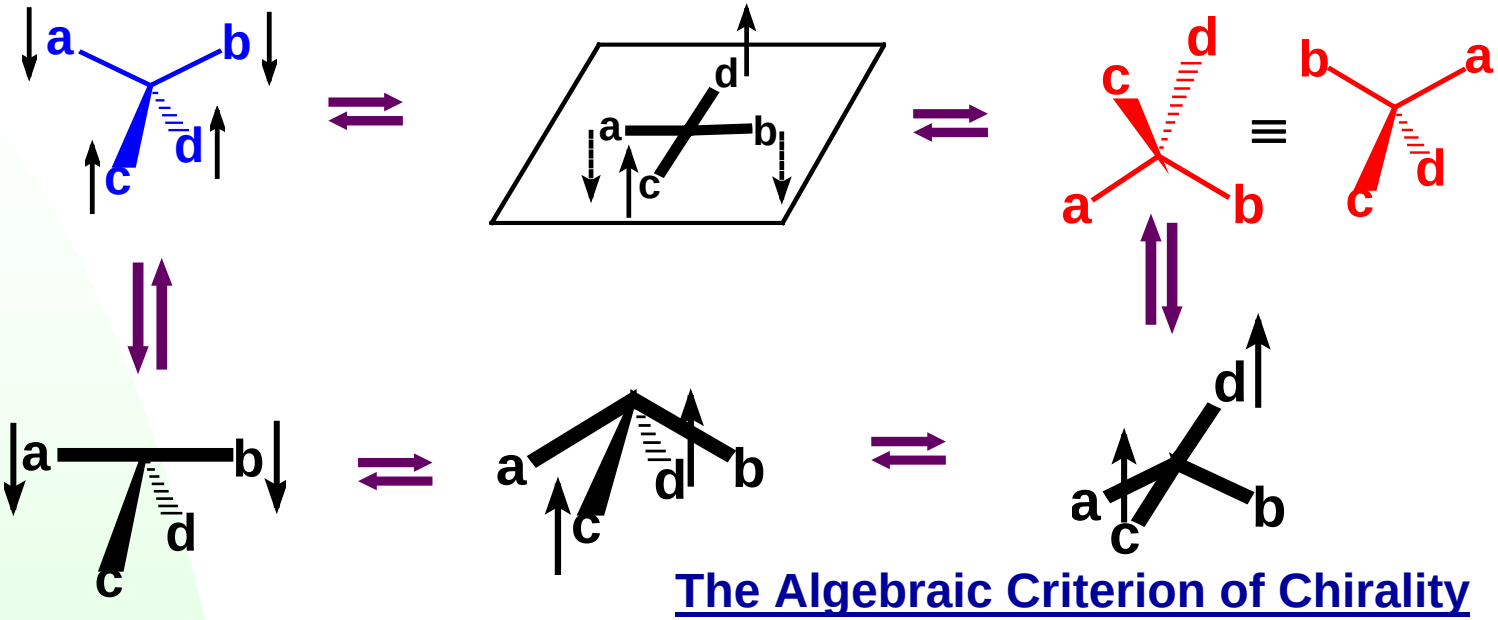


Conformationally-switched crowns:

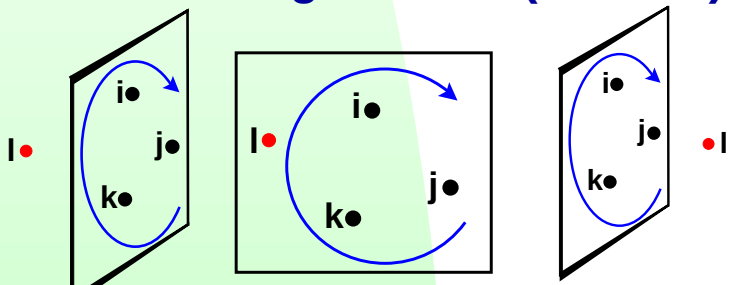


Stereochemistry and conformational analysis:
configuration

R-configuration



Point 3D-Configurations (3D-PCs)



$\psi[i,j,k,l] = -1$ $\psi[i,j,k,l] = 0$ $\psi[i,j,k,l] = +1$

$\psi[i,j,k,l] = -\psi[i,k,j,l]$

The Algebraic Criterion of Chirality

For any function $\psi[i,j,k,l]$ a unique antipode function, ψ: $\psi[i,j,k,l] = -\psi[i,k,j,l]$ necessarily exists. They can belong either to the same or to different equivalence classes.

There are TWO groups of automorphisms:

(a) the "normal" group $Aut(\psi)$ consists of (+)-automorphisms, which convert a given function into itself and

(b) the expanded group $Aut[\psi]$ which additionally contains (-)-automorphisms, converting a given function ψ into antipode function ψ.

If $Aut(\psi) = Aut[\psi]$ the functions ψ and ψ belong to the *different equivalence classes and corresponding configurations are chiral.*

V.N.Drozd, N.S.Zefirov, V.I.Sokolov, I.V.Stankevich, *Zh.Org.Chem.*, 1979, *15*, 1785; 1981, *17*, 233;
S.S.Tratch, N.S.Zefirov et. al., *J. Chem. Inf. Comput Sci.*, 1996, *36*, 448; *MATCH*, 2009, *61*, 217.

Mathematical chemistry and computer science

"...every attempt to employ mathematical methods in the study of chemical questions must be considered profoundly irrational and contrary to the spirit of chemistry. . ."

Auguste Comte, 1830

- **Development of "*formal-logical approach*" as the basis for (a) classification of organic reactions, (b) search for novel reactions (reaction design), (c) non-empirical computer-assisted synthesis.**

Lomonosov Award 1983 (MSU)

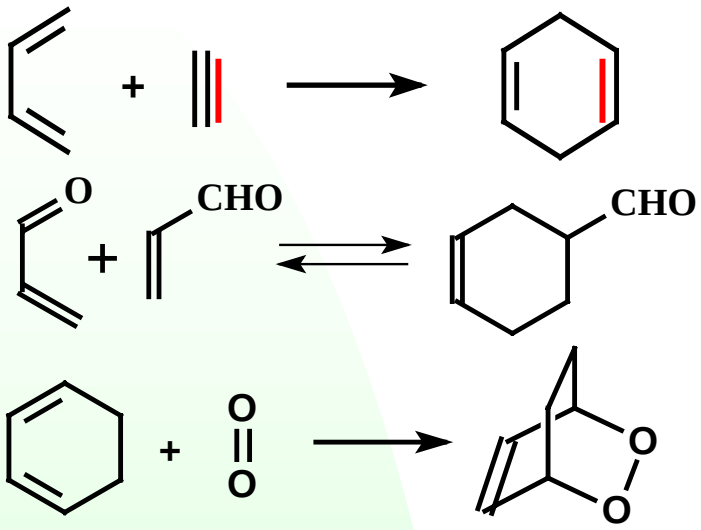
- **QSAR. Inverse problem in QSAR. The problems of topological description of molecules. Topological and fragmental indices. Graph theory in application to chemistry. Structural design, structural generators. Neural networking.**

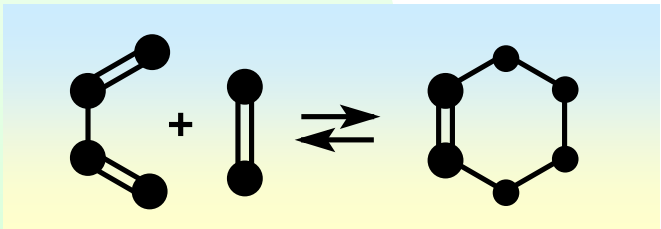
- **Creation of novel computer algorithms, programs and program complexes to solve chemical problems.**

Mathematical chemistry and computer science:

Formal-logical approach (*Zhur.Org.Chem.*, 1982,*18*,1561)

Symbolic equation:

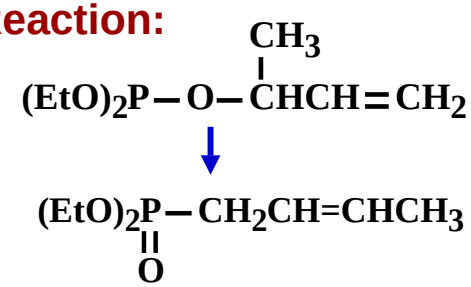




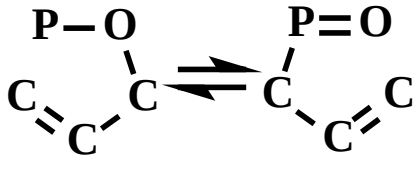
How many symbolic equations exists in a whole organic chemistry?

Extraction of symbolic equations from experimental data

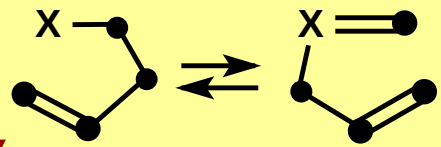
Reaction:



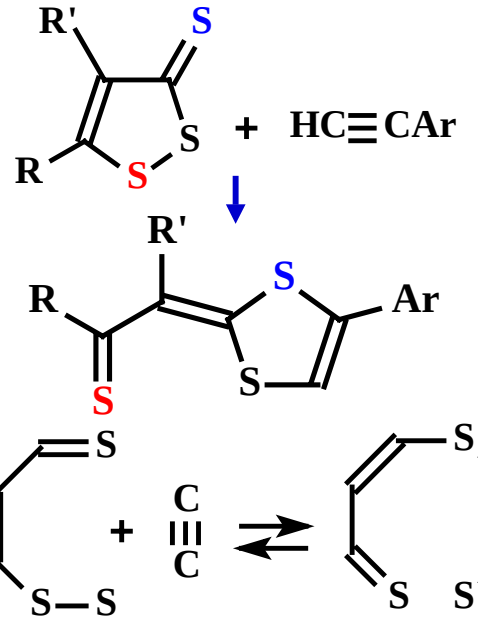
Reaction equation:

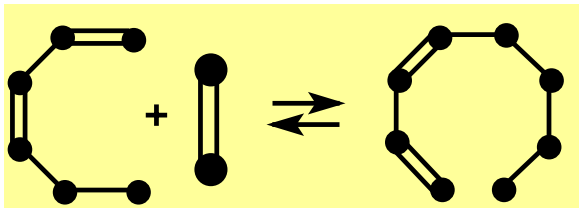


Symbolic equation :



Sigmatropic rearrangement





[2+(1.5)]-sigmatropic addition

SYMBEQ: N.S. Zefirov, I.I. Baskin, V.A. Palyulin, *J. Chem. Inf. Comput. Sci.*, 1994, *34*, 994. **ARGENT**: N.S. Zefirov, S.S.Tratch, M.S.Molchanova, *MATCH*, 2002, *46*, 253, 275; *J.Phys.Org.Chem*, 2003, *16*, 463.

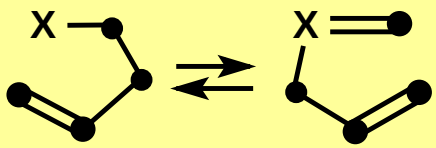
MSU Chem. Dept.

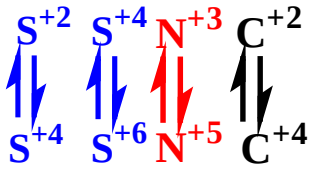
IPhAC RAS

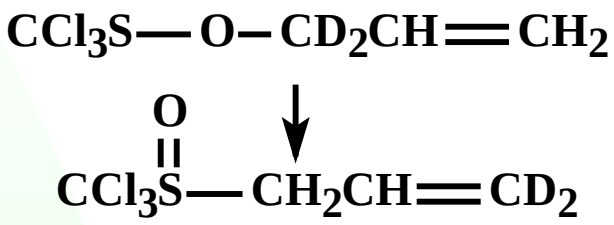
Mathematical chemistry and computer science:

Formal-logical approach

Symbolic equation:

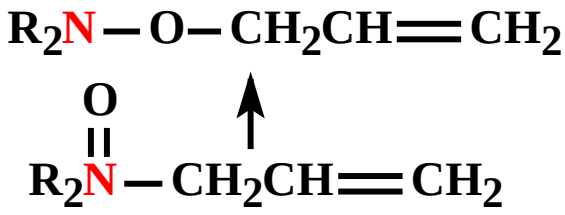


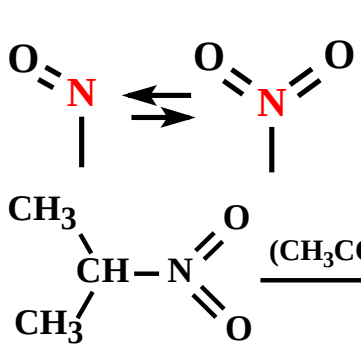


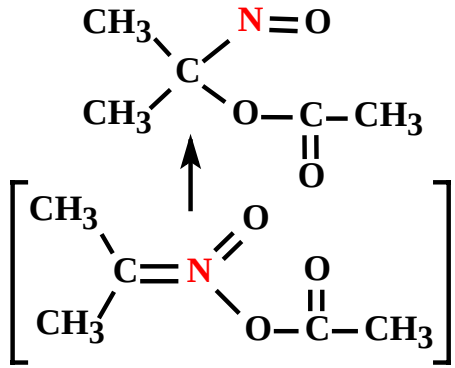


Mislow K. *JACS*, 90, 4861 (1968)
Braverman S. *Israel J.Chem.* 5,125(1967)
Zefirov N.S. et. al. *Vestnik Moscow Univ.*, 135 (1969); *Zh.Org.Khim.*,7, 947 (1971)

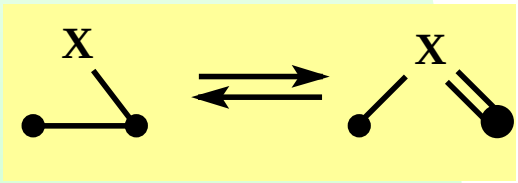
Meisenheimer (1919)



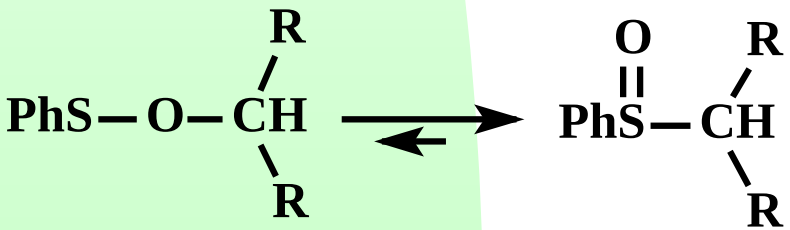




Zefirov N.S., et. al. *Zh.Org.Khim.*, 38,1484 (2002)

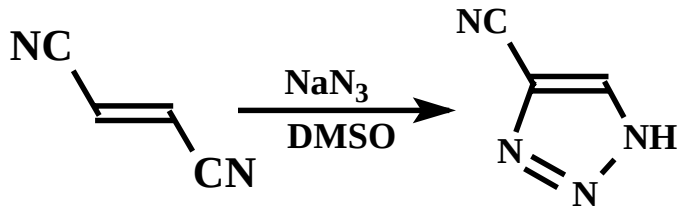


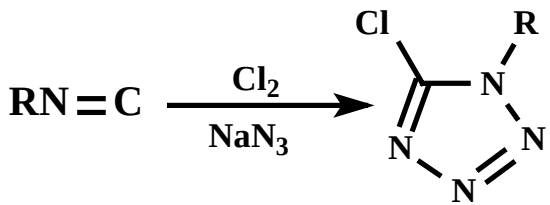
Zefirov N.S. et. al. *Zh.Org.Khim.*,8, 433 (1972)



R = Ph, cyclo-C_3H_5

ibid., 4, 722, 1300 (1968); 6, 2596 (1970); 8, 1335, (1972); *J.C.S., Chem. Comm.*, (1971), 1001.





Mathematical chemistry and computer science: *QSAR*

(Quantitative Structure-Activity) and QSPR

1. Set of compounds with known activity has to be subdivided into training set and test set .
2. Set of descriptors, which are believed to adequately characterize the property, has to be estimated.
3. The correlation of the selected descriptors and property has to be traced for training set using statistical methods
4. The validation of the constructed model/s on the test set of compounds with known properties.

Topological indices

I. Stankevich, M.Stankevich, N.Zefirov, *Usp.Khim.*, 1988, *57*, 337

Connectivity indices [Randic, χ; Kier-Hall, κ], Wiener index [W], Tratch-Stankevich-Zefirov (expanded Wiener index), Balaban and Gutman indices, Hosoya index, Merrifield index, solvatation index (Zefirov-Palyulin), information indices.

Phisico-chemical

Oliferenko A.A., Palyulin V.A., Zefirov N.S., *J.Phys. Org. Chem.*, 2001, *14*, 355 ; *SAR,QSAR Env. Res.*, 2002, *13*, 297

Indices based on electronegativities, electrotopology, atomic charges (e.g. Gasteiger charges, Zefirov charges), Van-der Waals volumes and surfaces, descriptors of H-bonds, lipophilicity.

Quantum-chemical

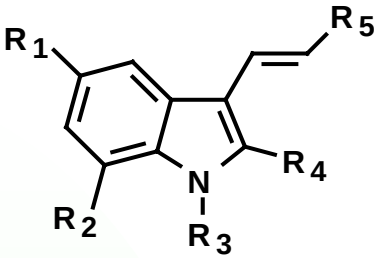
A.R.Katritzky et al., *Chem. Rev.*, 1996, 96, 1027

Charges, HOMO-LUMO-energies, superdelocalisability, atom-atom and molecular potentials, orbital and electron dencities, dipole moments, polar indices.

Fragmental (subgraph) descriptors

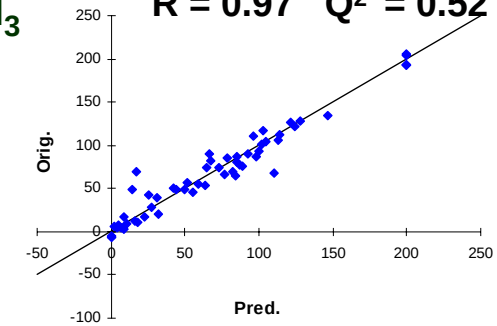
N.Zhokhova,A. Zefirov, V. Palyulin, N. Zefirov, *J. Chem. Inf. Comput. Sci.*, 2002, *41*, 1112; *Изв. РАН*, 2003, 1005.

QSAR: inhibition of intake of Ca^{2+} by indoles

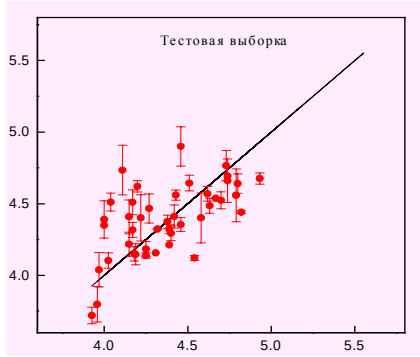


R = CH_3, Et
R_1 = Hal, CH_3, OCH_3
R_2 = CH_3, Et

Training set : 57 structures
R = 0.97 Q^2 = 0.52



Test set



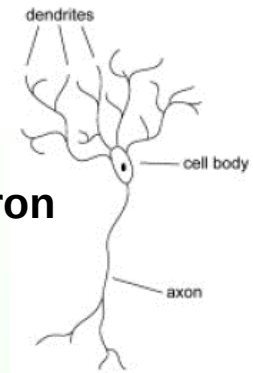
Modeled activity - $(K_4-K_3) / (K_2-K_1)$
$^{45}Ca^{2+}$ uptake inhibition in synaptosomes:

K_1 – Ca^{2+} K_2 – Glu + Ca^{2+}
K_3 – test compound + Ca^{2+}
K_4 – test compound + Glu + Ca^{2+}

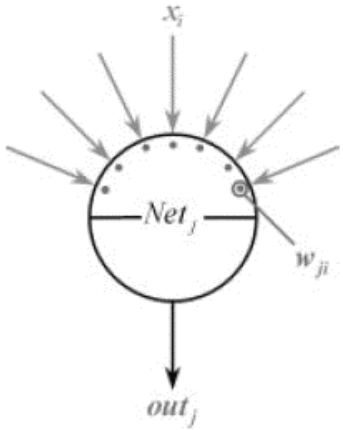
NT-1515

1. **QSAR-models:** (1) b.p.; (2) flash point; (3) m.p.; (4) retention indices ; (5) pKa; (6) solubility; (7) heat of solvatation; (8) heat of formation;(9) enthalpy of sublimation and vaporization; (10) magnetic susceptibility; (11) polarizability; (12) lipophilicity; (13) rate constants of homolysis and impact sensitivity of nitrocompounds; (14) affinity of dyes for the cellulose fiber; (15) mutagenicity; (16) toxicity; (17) diffusion in rubber; (18) refraction: (19) neural net models for calculation of Hammett and Taft constants; (20) inhibition of serine esterases; (21) octane number etc.
2. Calculating schemes for partial atomic charges to reproduce electrostatic potential.
3. Neural network and “support vector machine”.

Mathematical chemistry and computer science:
neural networking

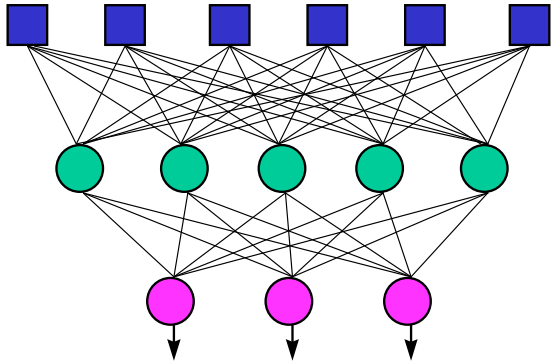


Neuron



Artificial neuron

Neural net with two layers of active neurons.

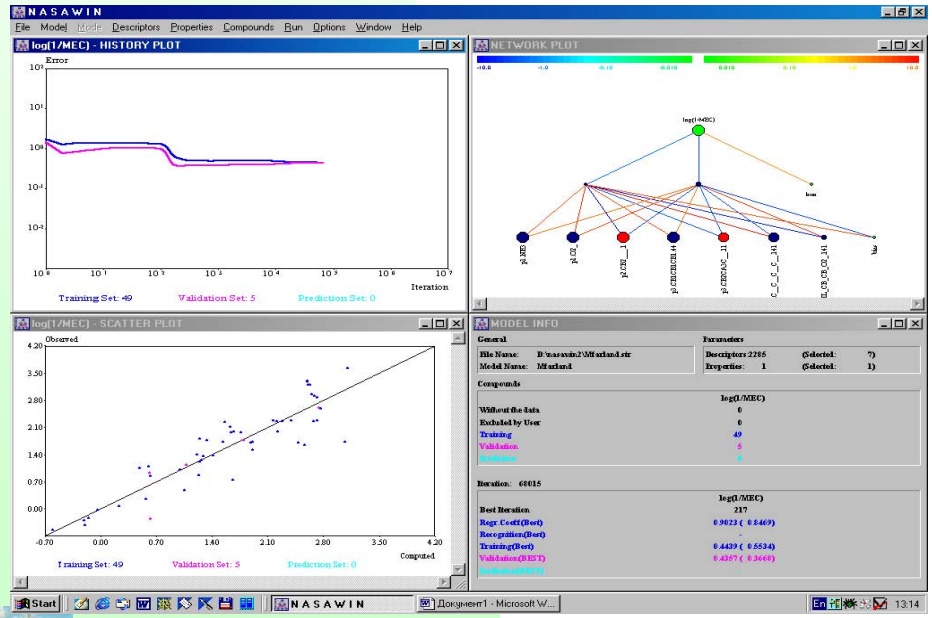


Entrance layer

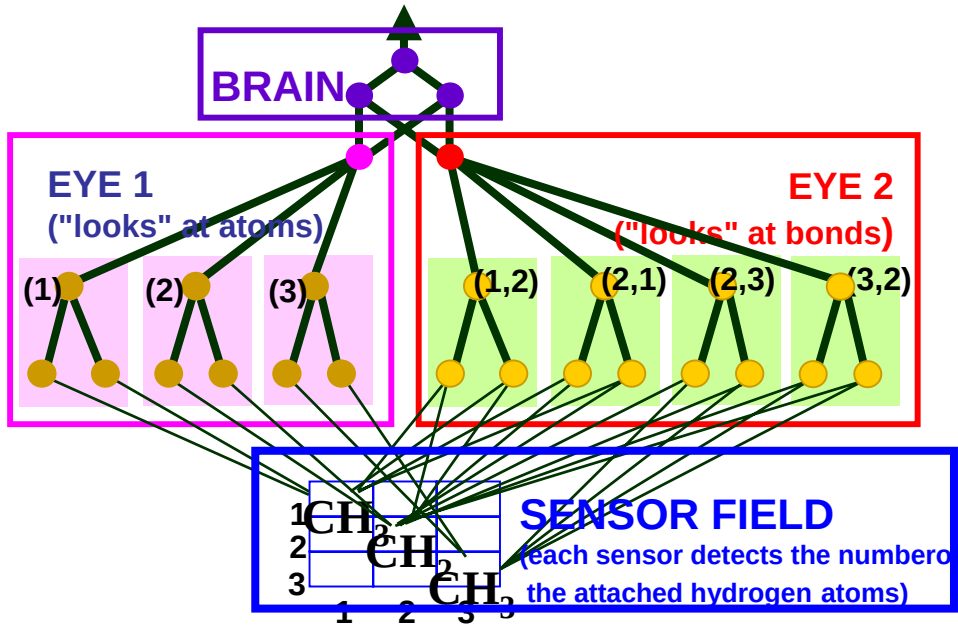
Hidden layer

Out layer

Program complex NASAWIN:
anticococidal activity of triazines



Architecture of the Neural Device for Direct QSAR
(in application to the propane molecule) :



Baskin, I. I.; Palyulin, V. A.; Zefirov, N. S. et al., *J. Chem. Inf. Comput. Sci.*, 1997, *37*, 715; *SAR QSAR Env. Res.*, 2001, *12*, 401; 2002, *13*, 35; *Usp.Khim.*, 2003, *72*, 706.

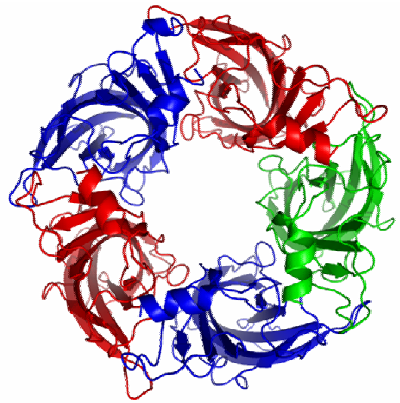
Medicinal chemistry

“BIOTARGET”

Enzyme, receptor, ion channel and related biological structures, which function/s in pathology are completely different from ones in a normal condition. *Drug* – compound selectively binding with particular biotarget.

- **QSAR, drug design and molecular modelling.**
- **Creation of novel computer algorithms, programs and program complexes for the effective prediction, structural search and selection of physiologically active compounds.**
- **Modeling of receptors.**

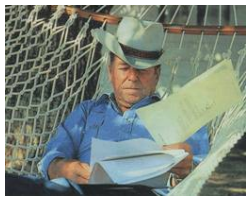
Benzodiazepine-binding center of $GABA_A$ receptor:



- **Anti-cancer, neuroprotector and cardioprotector compounds.**

Medicinal chemistry: problem of neuroprotectors and cognitive enhancers. Alzheimer desease.

Auguste D., 1906
(first patient)



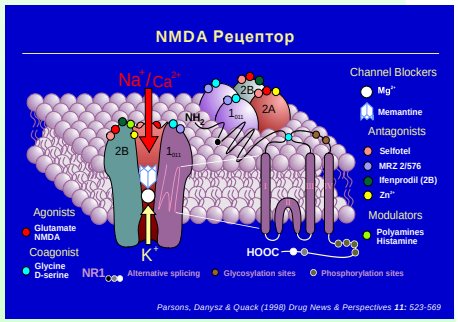
R. Reagan, 1990
(the famous patient)

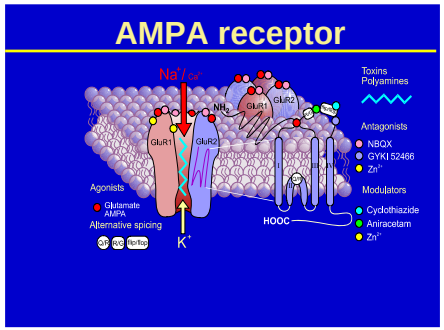
It affects up to 4% of people over the age of 65 and 30-35% or more of those over age of 85. Currently AD affects approximately 20 millions people over the world and imposes an annual economic burden about US $ 100 billion.

Bachurin S.O., Zefirov N.S., et.al.,. *Ann. NY Acad. Sci.*, 2001, 939; Rus. Pat. № 2140417 (1999)

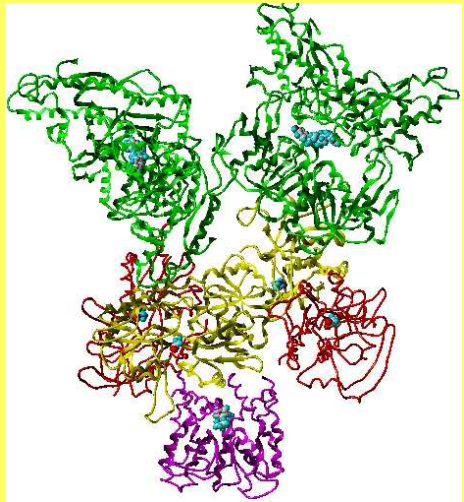
Glutamate receptors of CNS play key role for neurons plasticity and memory consolidation as well.

Hyperactivation of NMDA-subtype of these receptors leads to development of neurotoxicity. GOAL: simultaneous blocade of NMDA-receptors and activation of AMPA-receptors.





Computer molecular models of two ionotropic (NMDA and AMPA) and all metabotropic glutamate receptors

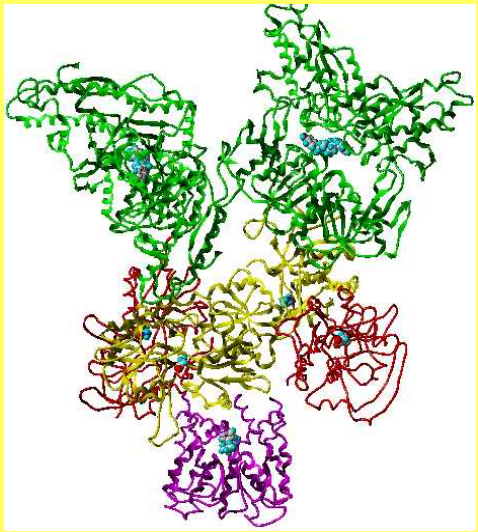


NMDA-receptor model

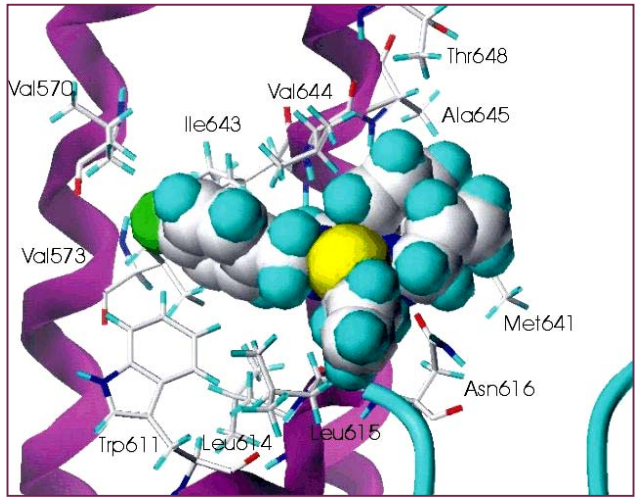
MSU Chem. Dept.

Palyulin, Zefirov, et.al., *J. Med. Chem.* 2003, *46*, 1609

Molecular models of NMDA и AMPA receptors. “Docking” of antagonists and blocators of ion channel. Aided design of multipuposed glutamatergic drugs

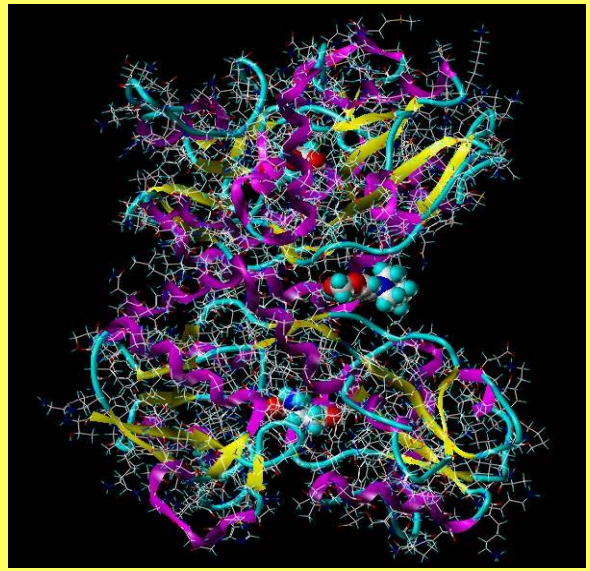


NMDA-receptor model



Virtual data bases screening (NMDA-receptor):

Data base size more 300000 structures

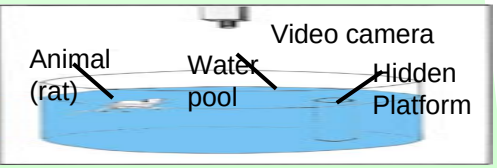


AMPA-receptor and “docking”

Virtual data bases screening (AMPA-receptor):

Data base size more 300000 structures

Transferred for pre-clinic study - 4



Animal test

Selected and synthesized compounds: appr. 600

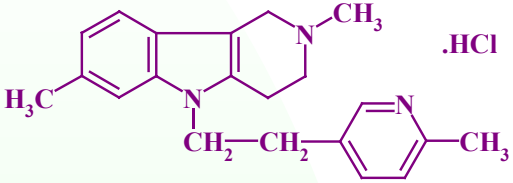
Palyulin, Zefirov et al., *J. Med. Chem.*, 2003, *46*, 1609;
Palyulin, Zefirov et al., *Dokl RAS*, 2004, *397*, 549.

MSU Chem. Dept.

IPhAC RAS

Dimebon – new Agent for treatment of neurodegenerative disorders

N.S.Zefirov, S.J.Bachurin et. al., *Russian Patent* № 2106864, 1998; № 2140417, 1999; United States Patent № 6,187,785 B1, 2001; European Patent № EP 0 876 818 B1, 2002.



PhAC RAS

MEDIVATION

Dimebon: august 2007 – "molecule of the month"

Сентябрь 03, 2008
Medivation received FDA permission to start test of Dimebon against Huntington disease.

Sept 03 , 2008 Pfizer and Medivation announced an agreement to develop and commercialize Dimebon. Medivation will receive $225 millions up-front payment, next milestone payment up to $ 500 millions plus undisclosed milestone payments.

SF BUSINESS TIMES | JUNE 17-23, 2005 sanfrancisco.

S.F. firm thinks Russian drug nothing to sneeze a

BY DANIEL S. LEVINE
dlevine@bizjournals.com

A fledgling San Francisco biopharmaceutical believes a Russian antihistamine may not only help runny noses, but halt the progression of Alzheimer's disease.
Medivation obtained the rights to Dimebon, which has a more than 20-year history in Russia as an antihistamine but has indications that it might be an effective new treatment for Alzheimer's disease. The company is launching a mid-stage clinical trial in Russia to establish human proof-of-concept of Dimebon as an Alzheimer's drug and is beginning animal studies in the United States to prepare for a filing with the U.S. Food and Drug Administration to begin clinical trials here.

MACHADO: Wants to diversify

The New York Times nytimes.com

June 11, 2007

Antihistamine Shows Promise in Treating Alzheimer's

By ANDREW POLLACK

A drug long used as an antihistamine in Russia is showing what some scientists characterize as surprisingly strong results in treating Alzheimer's disease.

"These are the best data that a Phase 2 Alzheimer's study has ever shown," Dr. Rachelle S. Doody of Baylor College of Medicine, the lead author of the study, said in an interview. Dr. Doody is a paid adviser to the drug's developer, Medivation.

Dimebon was approved as an antihistamine in Russia in 1983, but a scientist there then found it might work for Alzheimer's. Dr. David T. Hung, an entrepreneur in San Francisco, heard about this and started Medivation in 2003. The company's stock more than quadrupled after the results from the first six months of the trial were reported in September.

Dr. Jeffrey L. Cummings, director of the Alzheimer's disease center at the University of California, Los Angeles, said the effect of Dimebon was "larger than what we're seeing with any of the existing medications and it persists longer."

SAN FRANCISCO Business Times

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INDUSTRY WRAPUPS

Medivation receive US $ 725 M

San Francisco > Print Edition > Industries > Health Care - General

Friday, September 19, 2008

Biotech

'Diamond in the rough' at center of Pfizer-Medivation deal

San Francisco Business Times - by Ron Leuty

Forbes.com

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BusinessWire

Medivation Provides Business Update; Alzheimer's Program on Track; Team Expanded in Anticipation of Potential New Programs

05.18.05, 4:03 AM ET

Orion Acquisition Corp. II (OTCBB:MTMR), and its wholly owned subsidiary Medivation, Inc., today announced that activities related to the Company's Phase II clinical trial of Dimebon(TM) for the treatment of Alzheimer's disease (AD) are proceeding as scheduled and that its team is expanding in anticipation of potential new programs in other important disease indications.

The manufacture of Dimebon drug substance under good manufacturing practices (GMP) has been completed, and finished Dimebon tablets are currently being manufactured under GMP and are on schedule to be delivered to targeted centers in Russia in July. Based on this timeline, the Phase II trial should commence in the third quarter of 2005, and is anticipated to conclude in June 2006.

BC BLOGCRITICS MAGAZINE TV / FILM

"A SINISTER CABAL OF SUPERIOR WRITERS"

Blogcritics is an online magazine, a community of writers and readers from around the globe.

Publisher: Eric Olsen

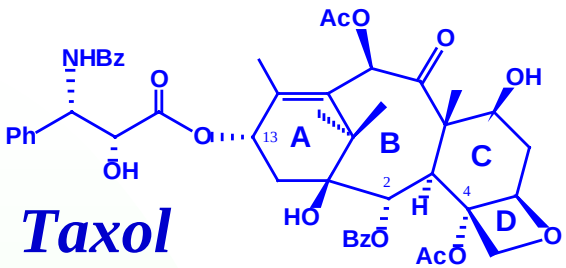
OPINION

***Boston Legal*, Alzheimer's, and Dimebon**

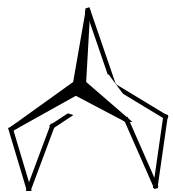
Written by Robert T DeMarco
Published December 04, 2008

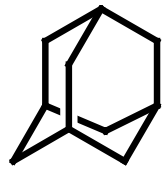
I am a fan of the show *Boston Legal*. For years the show has alluded to the mild c
impairment of Denny Crane (William Shatner) by referring to it as "mad cow." Mil

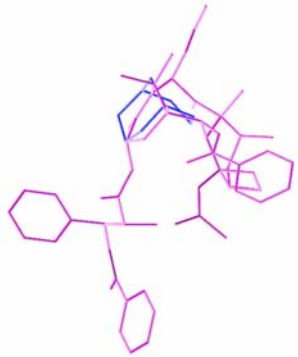
Medicinal chemistry: problem of antitumor compounds.

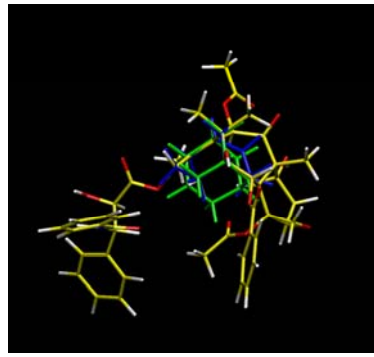


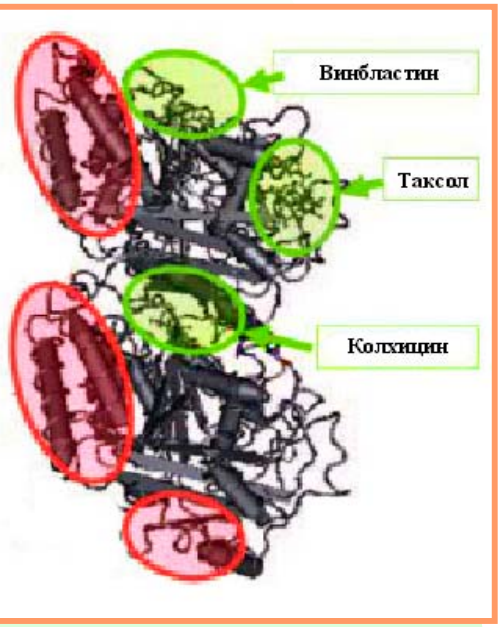
Taxol

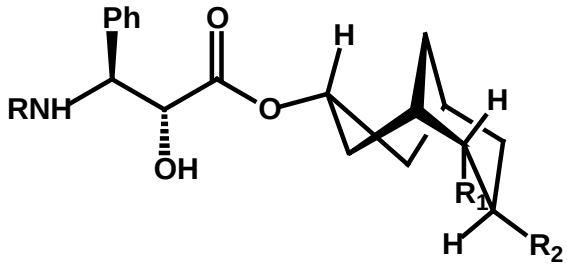


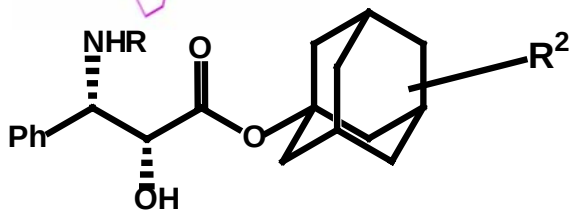




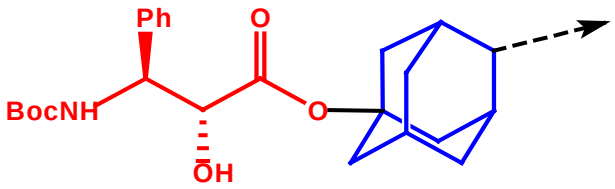


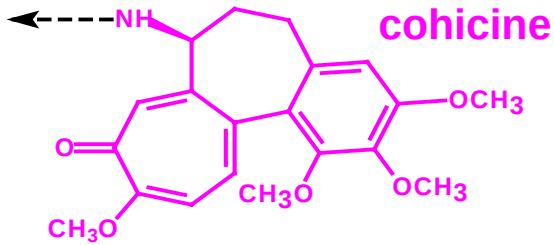


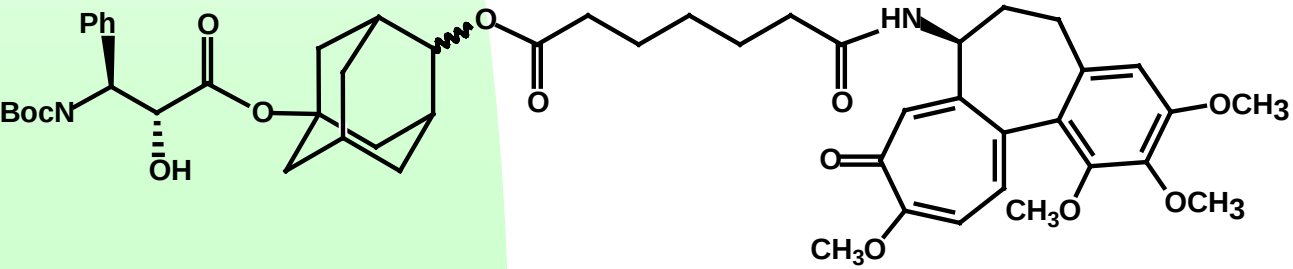




Creation of twin-drug:







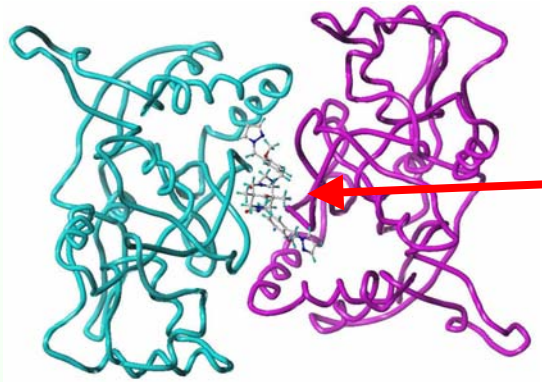
cytotoxicity against A 549 0.6 nM.

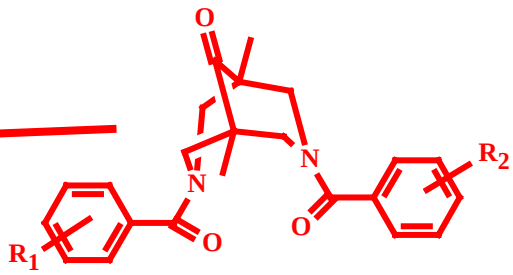
Double activity

Zefirova O.N., Zyk N.V., Zefirov N.S., et. al., *Mend.Comm.*, 2007, *17*, 332; 2008, *18*, 183; *Bioorg.Med.Chem.Lett.*, 2008, *18*, 5091.

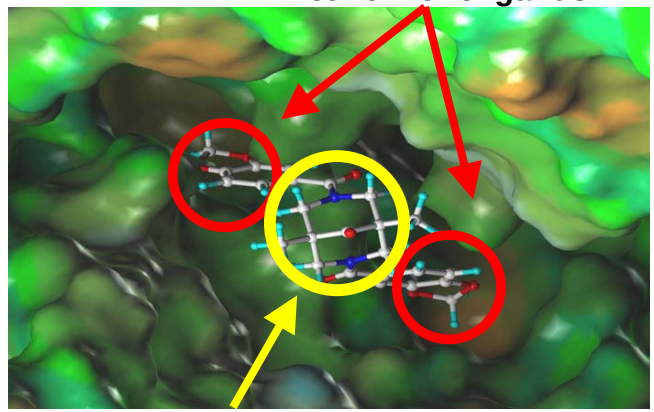
Medicinal chemistry : creation of twin-drug

Novel cognition enhancers using the ligands of AMPA-receptors (Moscow Univ., IPhAC RAS, INPh RAMS)





Active monoligands



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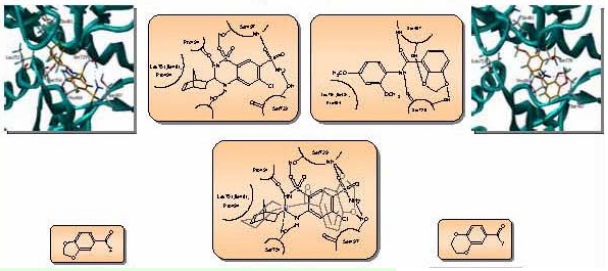
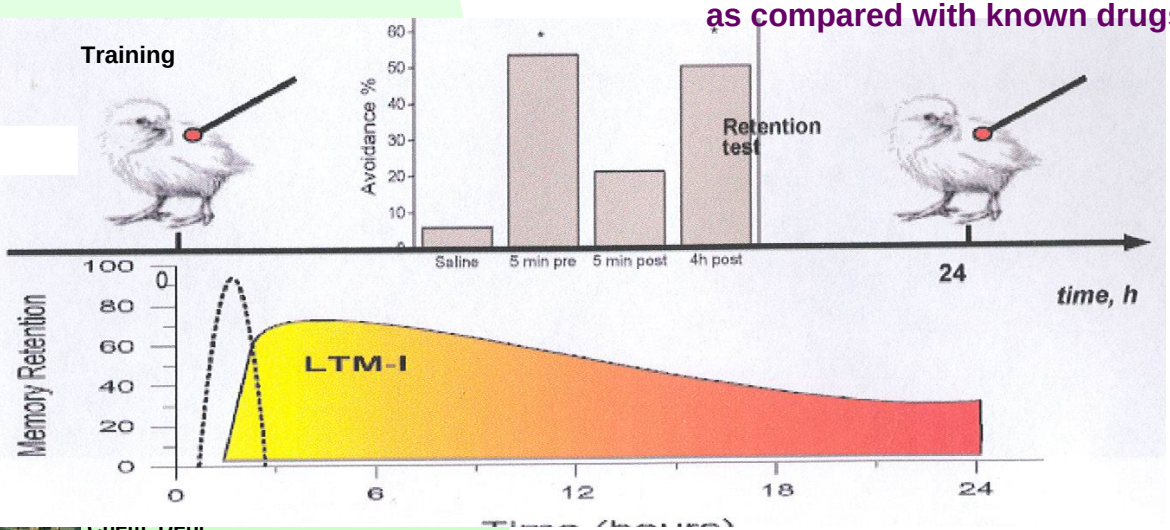


Series of molecules were constructed using molecular modelling having the optimal binding with receptor; the synthesis of them was performed3.

Experimental biological tests reveal record results – increasing of activity up to 10000 times as compared with known drugs.

1. They potentate AMPA-receptors at record-low pico-molar doses
2. They posses ability to “restore” lost memory (INPh named P.K. Anokhin, RAMS)



Patent RU 2 333 211 C1
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I am delighted to recognize all co-authors and the contributors to joint works and publications.

Thank You for attention