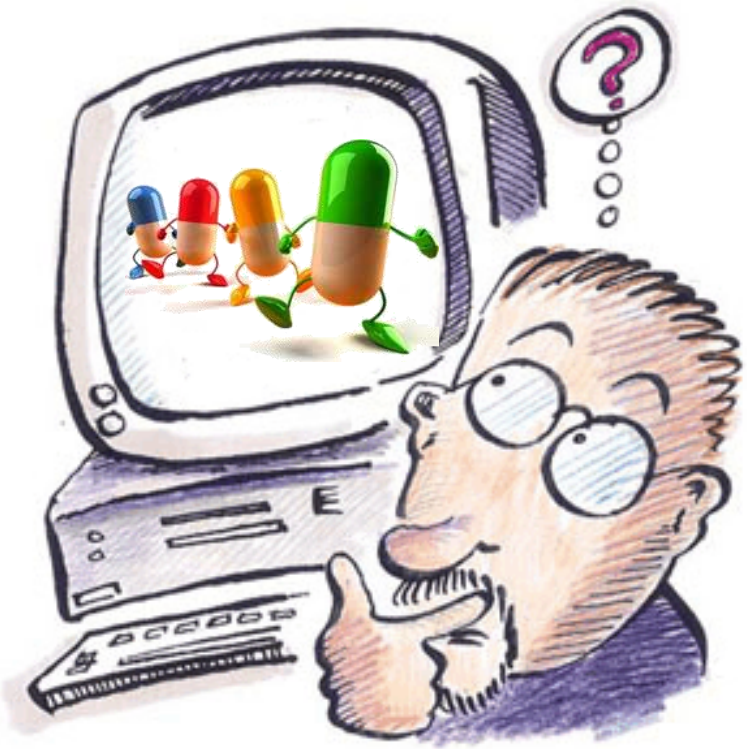
Računalne simulacije u modernoj kemiji i biokemiji



Robert Vianello

Grupa za računalnu organsku kemiju i biokemiju
Institut Ruđer Bošković
Zagreb, Hrvatska

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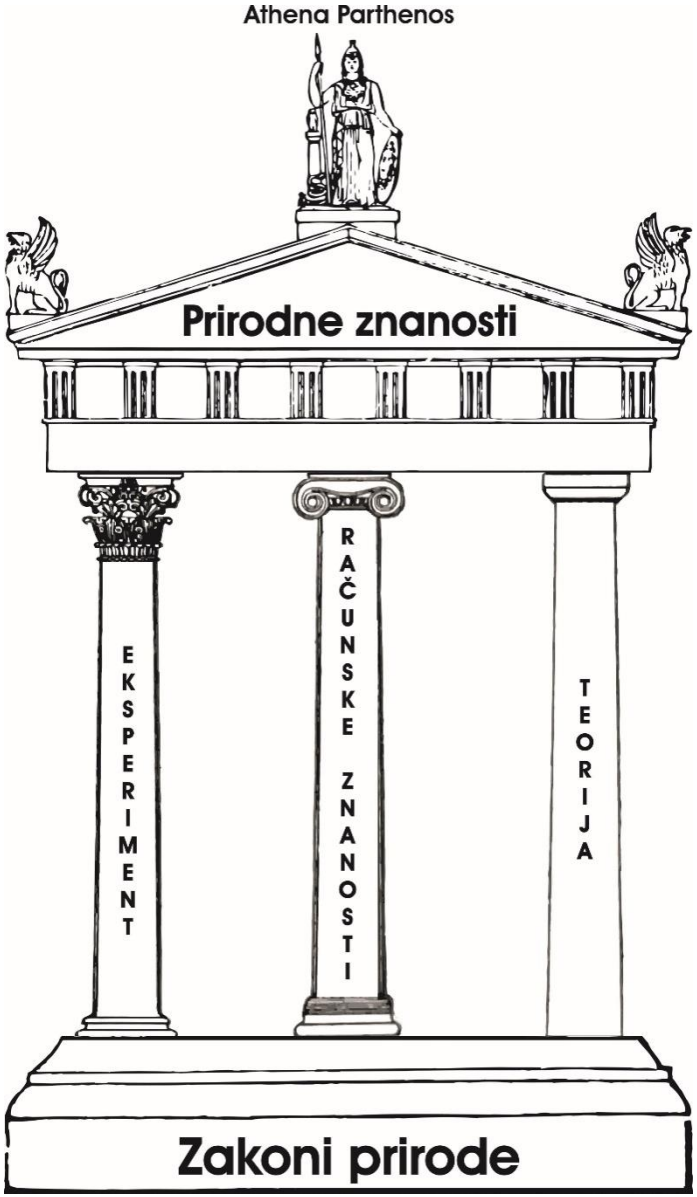


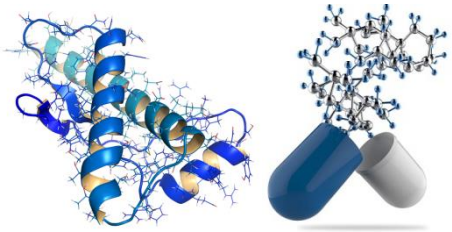
Računalna kemija

- **daje interpretaciju postojećih fenomena i pojava te omogućuje bolje razumijevanje podataka dobivenih eksperimentom** (uvid u elektronsku strukturu molekula nedostupnu eksperimentalnim uređajima)
- **pruža opis procesa nedostupnih eksperimentu** (spojevi izuzetno kratkog životnog vijeka, opasni spojevi, kemija u svemiru)
- **predviđa nove spojeve željenih svojstava i prije njihove sinteze**, čime ciljano vodi eksperimente prema novim materijalima
- **računalni rezultati vrlo su precizni** (usporedivi s onima dobivenim najsuvremenijim instrumentima)
- **ravnopravan, a često i nužan partner u eksperimentalnim istraživanjima** u svim granama kemije i znanostima o životu

Računalne simulacije u modernoj kemiji i biokemiji

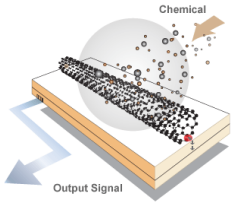
Struktura i funkcija bioloških sustava

- Vezanje supstrata i inhibitora u aktivno mjesto
- Mehanizam katalitičke aktivnosti i inhibicije
- Aktivacija receptora
- Mutirani enzimi
- Dizajn lijekova



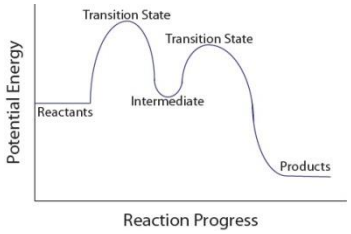
Dizajn novih materijala poboljšanih svojstava

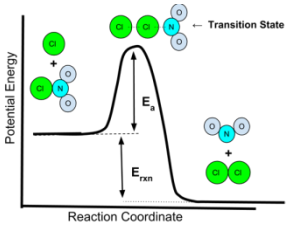
- Optički kemijski senzori i senzorski materijali
- Gelovi ionskih tekućina
- Jake organske superkiseline i superbaze
- Antioksidansi



Mehanizmi reakcija u organskoj kemiji

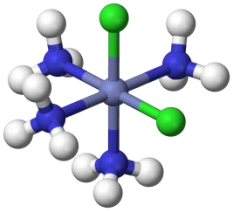
- Nukleofilne/elektrofilne adicije/supstitucije
- Kiselo-bazne reakcije
- Reakcije pregradnje u masenoj spektrometriji

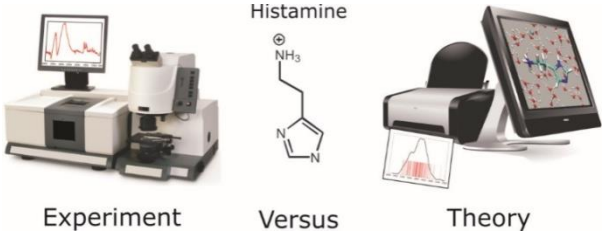




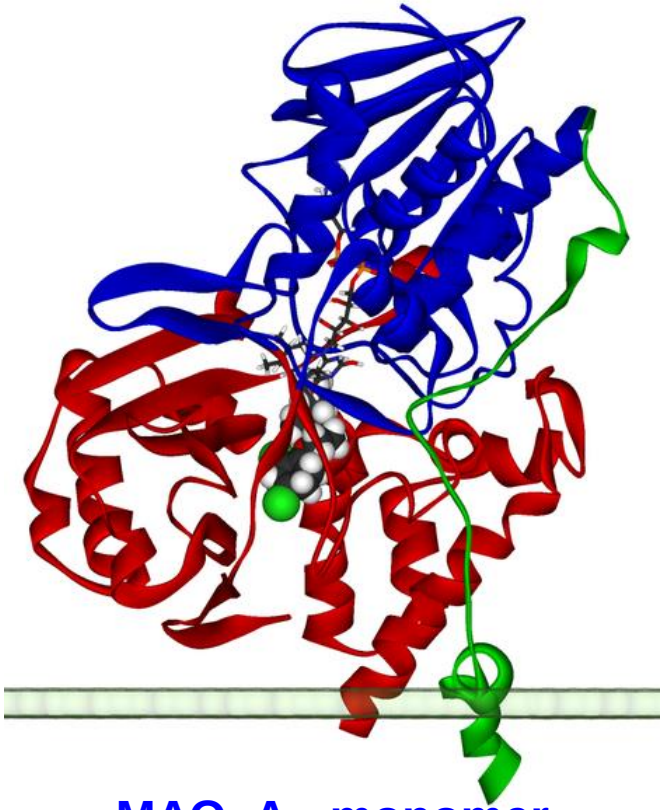
Struktura i svojstva malih molekula

- Metalni kompleksi
- Interakcija malih molekula s biološkim sustavima
- Vibracijska spektroskopija u kondenziranim fazama

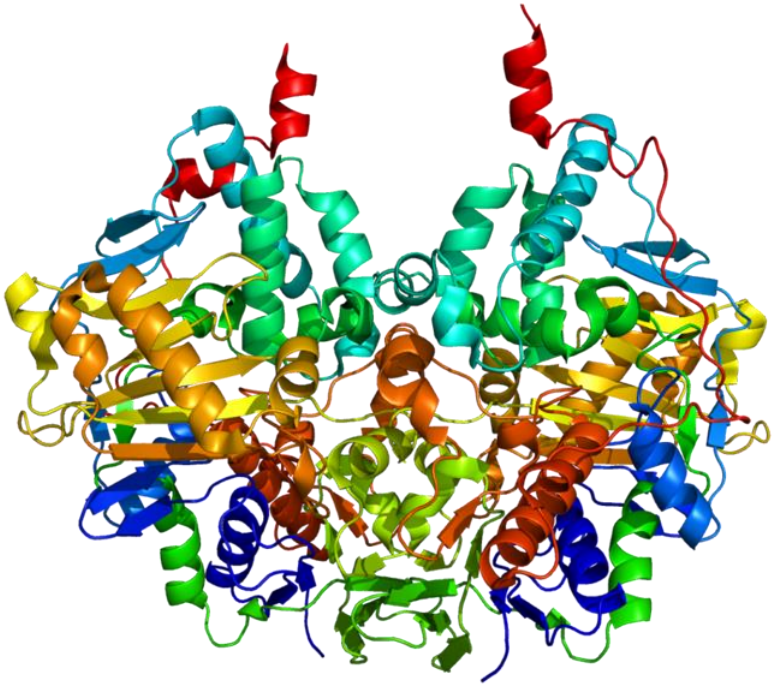




Monoaminoksidaza (MAO) – enzim za razgradnju amina u mozgu



MAO–A - monomer



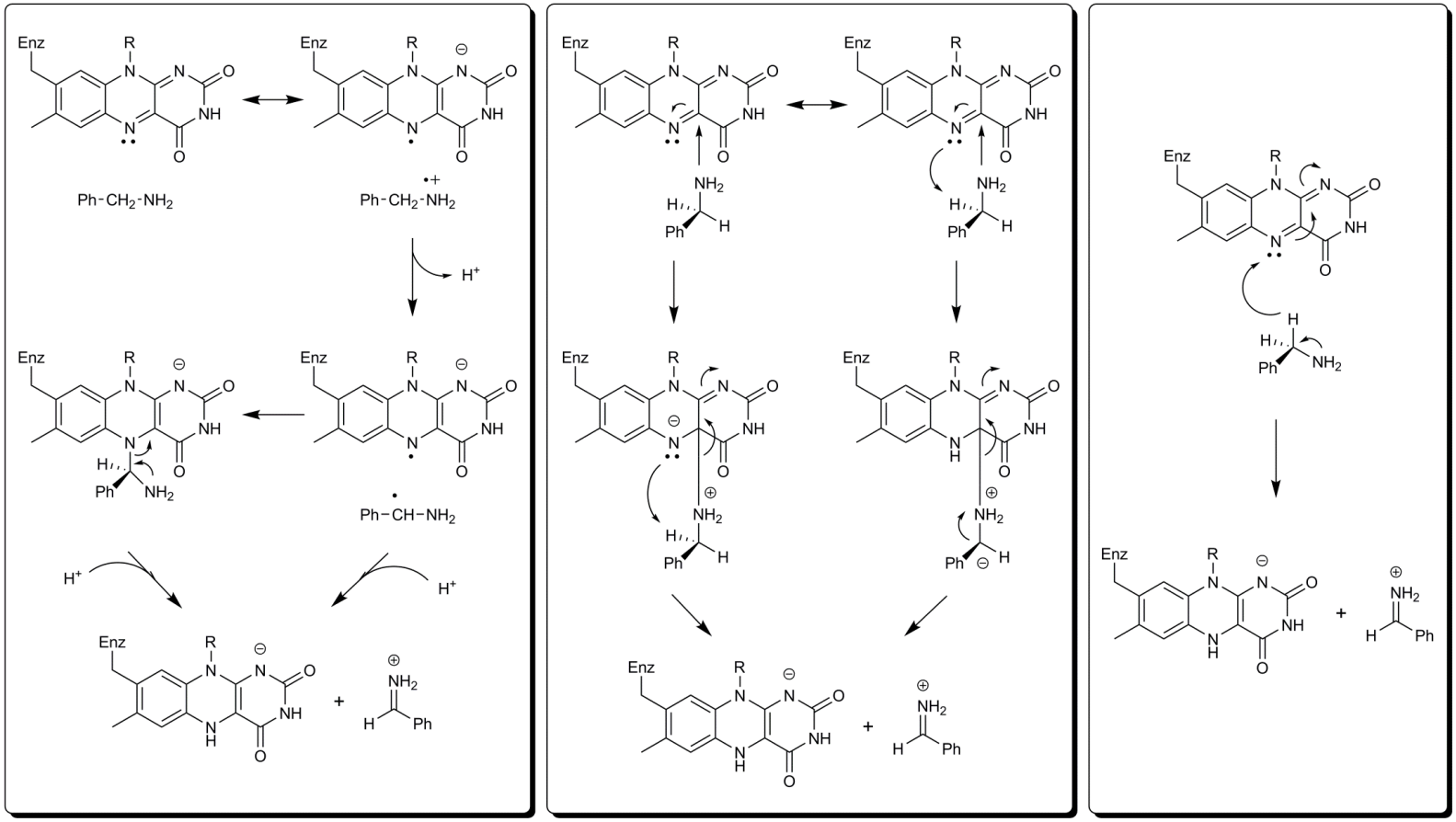
MAO–B - dimer

L De Colibus, M Li, C Binda, A Lustig, DE Edmondson, A Mattevi, *Proc Natl Acad Sci USA* **2005**, *102*, 12684.

S-Y Son, J Ma, Y Kondou, M Yoshimura, E Yamashita, T Tsukihara, *Proc Natl Acad Sci USA* **2008**, *105*, 5739.

C Binda, P Newton-Vinson, F Hubálek, DE Edmondson, A Mattevi, *Nat Struct Biol* **2002**, *9*, 22.

(a) RADICAL MECHANISM (b) POLAR NUCLEOPHILIC MECHANISM (c) HYDRIDE MECHANISM



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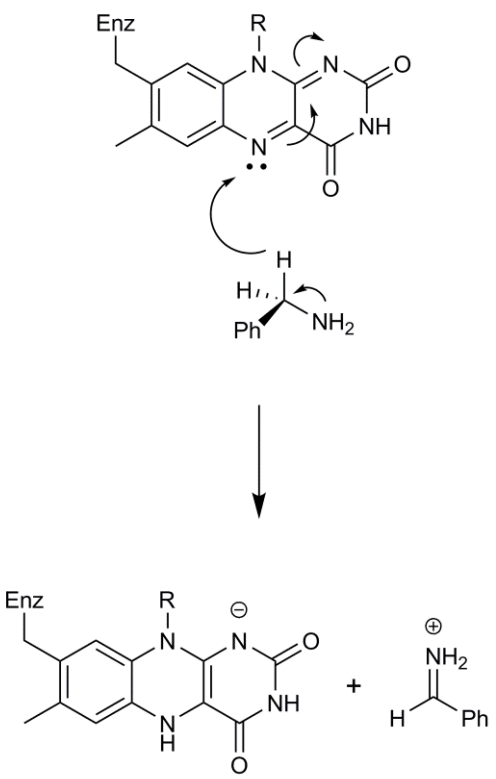
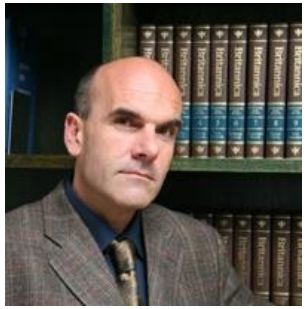
Atlanta, USA



HIDRIDNI MEHANIZAM



EurJOC European Journal of Organic Chemistry — FULL PAPER

DOI: 10.1002/ejoc.201201122

How are Biogenic Amines Metabolized by Monoamine Oxidases?

Robert Vianello,*[a] Matej Repič,[b] and Janez Mavri[b,c]

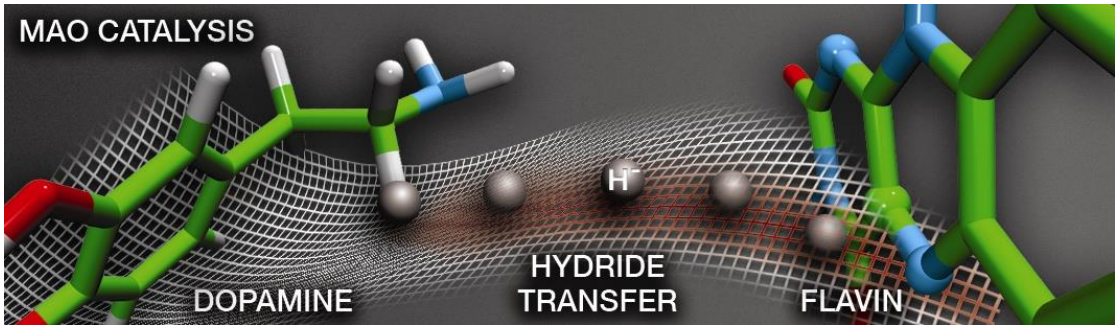
Keywords: Enzyme catalysis / Computer chemistry / Metabolism / Flavoenzymes / Oxidoreductases

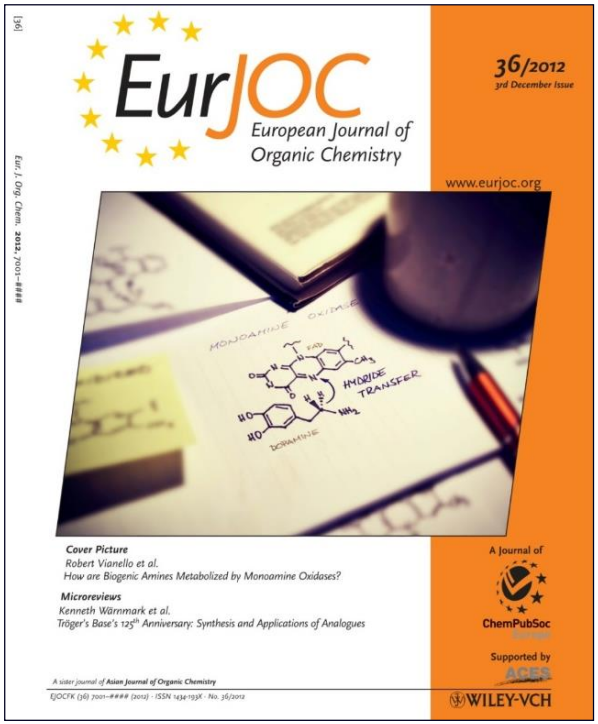
Monoamine oxidases (MAOs) are flavoenzymes important in regulating amine neurotransmitter levels and are the central pharmacological targets in treating depression and Parkinson's disease. On the basis of quantum chemical calculations, we have proposed a new two-step hydride mechanism for the MAO-catalysed oxidative deamination of amines. In the rate-limiting first step, through its N5 atom, the flavin abstracts a hydride anion from the substrate α-carbon atom and forms a strong covalent adduct with the thus created cation. This is followed by flavin N1 deprotonation of the substrate amino group, facilitated with two active-site water molecules, to produce fully reduced flavin, $FADH_2$, and neutral imine. We have demonstrated that our mechanism is in agreement with available experimental data and provided evidence against both traditional polar nucleophilic and single-electron radical pathways. These results provide valuable information for mechanistic studies on other flavoenzymes and for the design of new antidepressants and antiparkinsonian drugs.

Eur. J. Org. Chem. **2012**, *36*, 7057–7065

Katalitička aktivnost MAO enzima

- MAO razgrađuje amine do imina kroz **hidridni mehanizam** u 2 stupnja
- Interpretirana **katalitička aktivnost** MAO A i MAO B izoformi s nizom supstrata, racionaliziran efekt brojnih **točkastih mutacija**, reproduciran utjecaj **deuteracije** i **kinetičkih izotopnih efekata**
- Izračunate **pK_a vrijednosti** aminokiselina u aktivnom mjestu te pokazano da oba izoforma koriste **isti hidridni katalitički mehanizam**
- Interpretirana **selektivnost MAO enzima** te identificirane aminokiseline odgovorne za **vezanje supstrata** i **pravilnu orijentaciju** unutar aktivnog mjesta, što omogućuje primjenu u području **biotehnologije i proteinskog inženjerstva** te otvara prostor dizajnu i pripravi **novih MAO inhibitora**





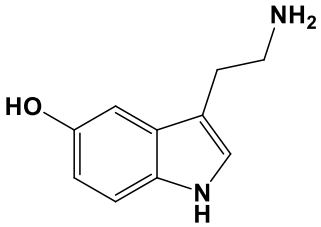
Eur J Org Chem **2011**, *32*, 6419
Eur J Org Chem **2012**, *36*, 7057
J Chem Theory Comput **2012**, *10*, 3864
J Phys Chem B **2014**, *118*, 4326
J Phys Chem B **2016**, *120*, 11419
Mol Neurobiol **2016**, *53*, 3400
Front Neurosci **2016**, *10*, 327
Chem Eur J **2017**, *23*, 2915
ACS Omega **2018**, *3*, 3665

MAO selektivnost u mozgu

MAO

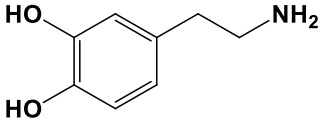
MAO A

MAO B



serotonin

dopamin

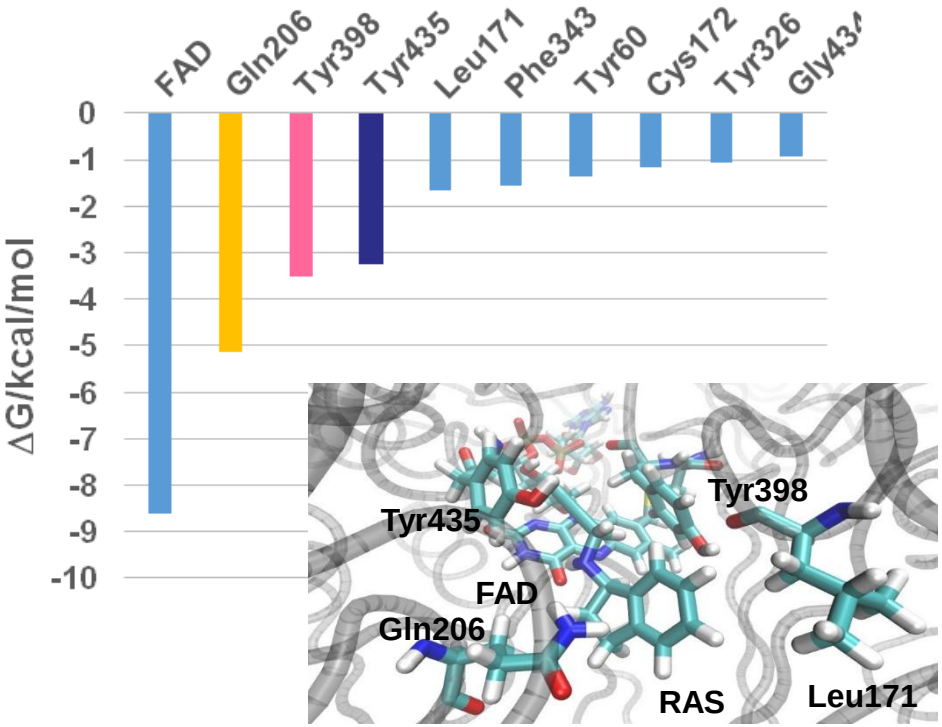


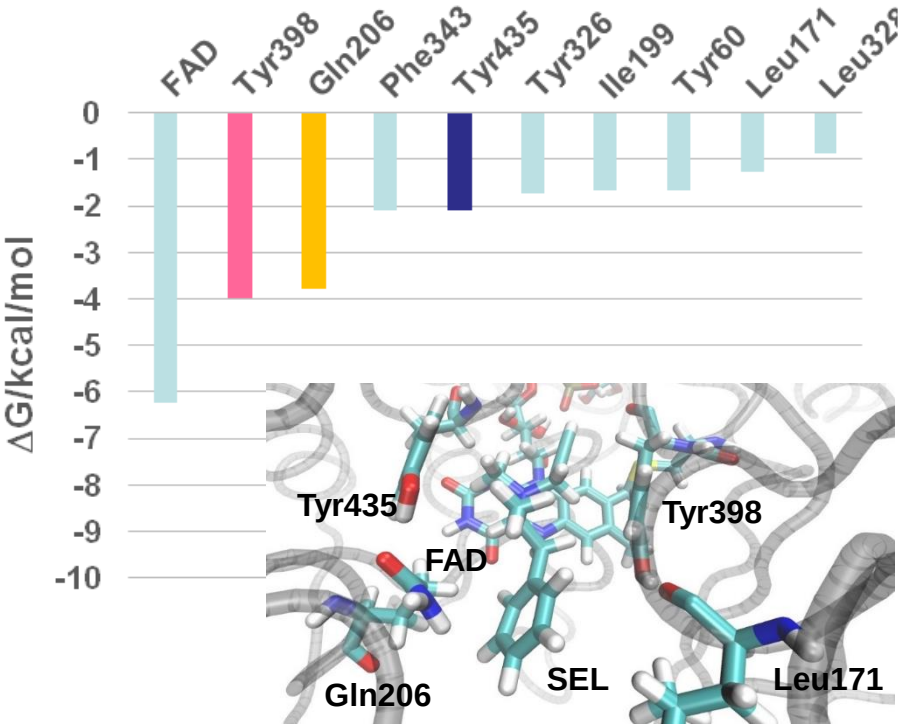
klorgilin

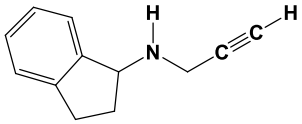
rasagilin
selegilin

DEPRESIJA

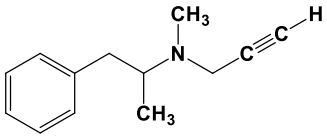
PARKINSONOVA BOLEST







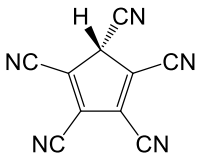
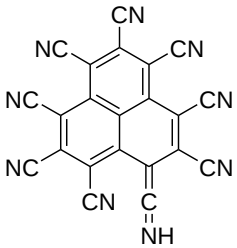
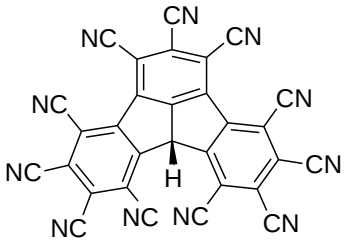
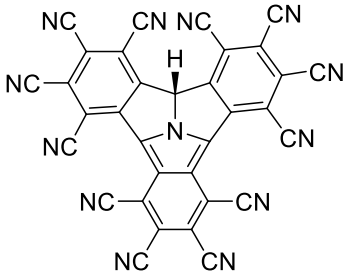
rasagiline (**RAS**)

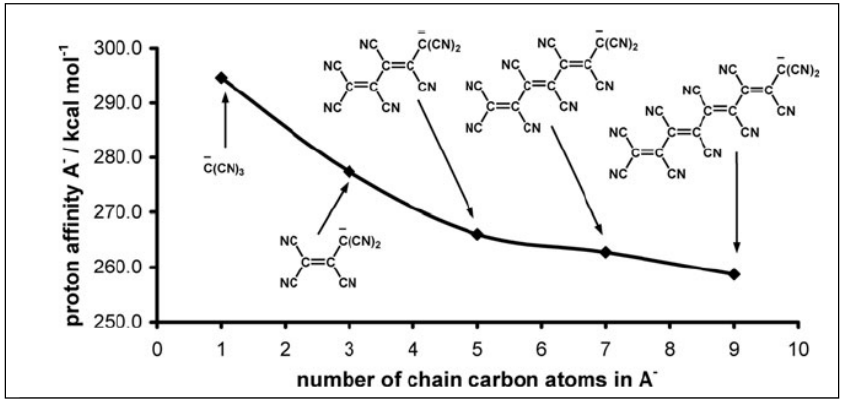


selegiline (**SEL**)

–27.0 kcal mol^{-1}	**$\Delta G_{BINDING}$**	**–31.9 kcal mol^{-1}**
1.4 · 10^{-8} M	**IC_{50}**	**6.8 · 10^{-9} M**

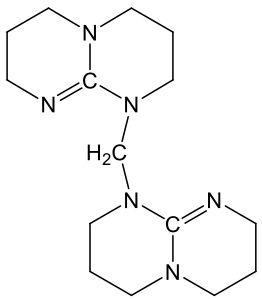
Dizajn novih materijala – jake organske superkiseline (policijano spojevi)

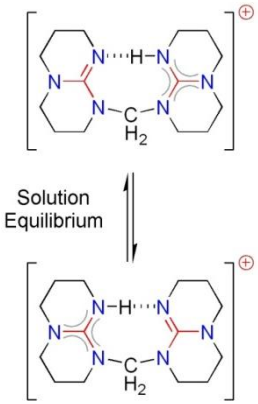
	H_2SO_4	$HClO_4$				
ΔH_{acid} (kcal/mol)	309.6	299.9	263.5	254.6	246.3	242.8

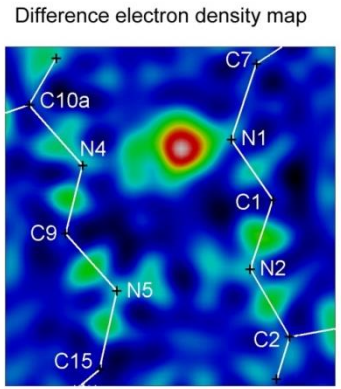


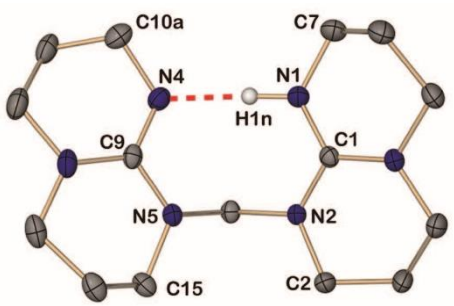
Int. J. Quant. Chem. **2018**, in print
J. Org. Chem. **2010**, *75*, 7670–7681
New J. Chem. **2009**, *82*, 27–39
New J. Chem. **2009**, *33*, 739–748
Chem. Commun. **2005**, *27*, 3412–3414

Dizajn novih materijala – jake organske superbaze (ciklički gvanidini)

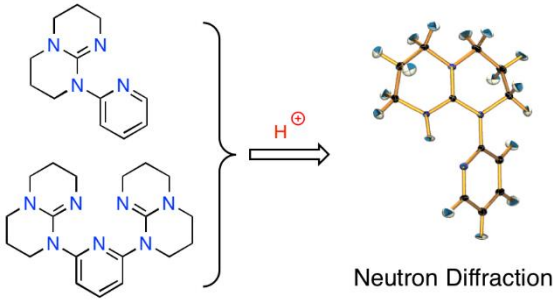


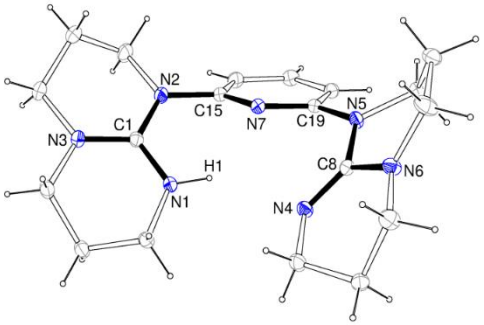






pK_a(MeCN) = 29.0

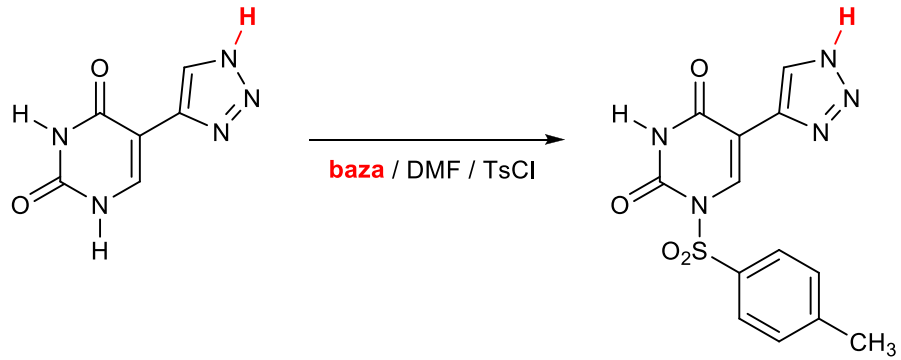


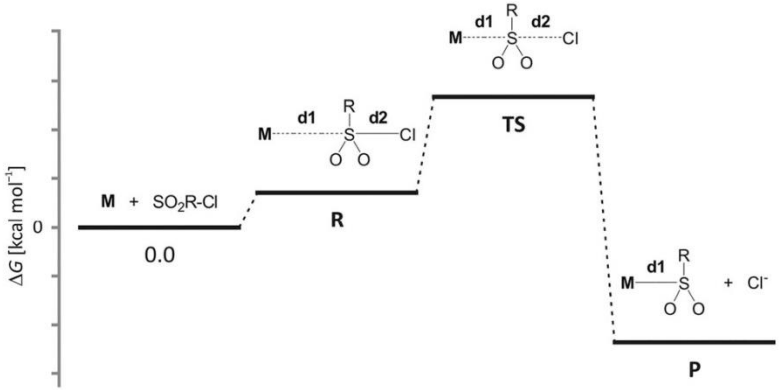


pK_a(MeCN) = 24.1; 25.6

J. Phys. Chem. A **2018**, *122*, 1464–1471
Eur. J. Org. Chem. **2017**, *30*, 4475–4489
J. Org. Chem. **2016**, *81*, 7612–7625
Chem. Commun. **2014**, *50*, 10941–10944
Chem. Rev. **2012**, *112*, 5240–5270
J. Am. Chem. Soc. **2009**, *131*, 16858–16868.

Sinteza 5-triazouracila i njihovih N[1]-sulfonil derivata

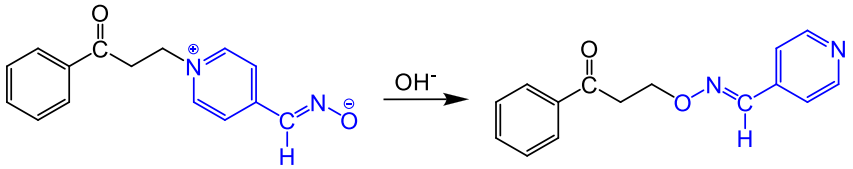




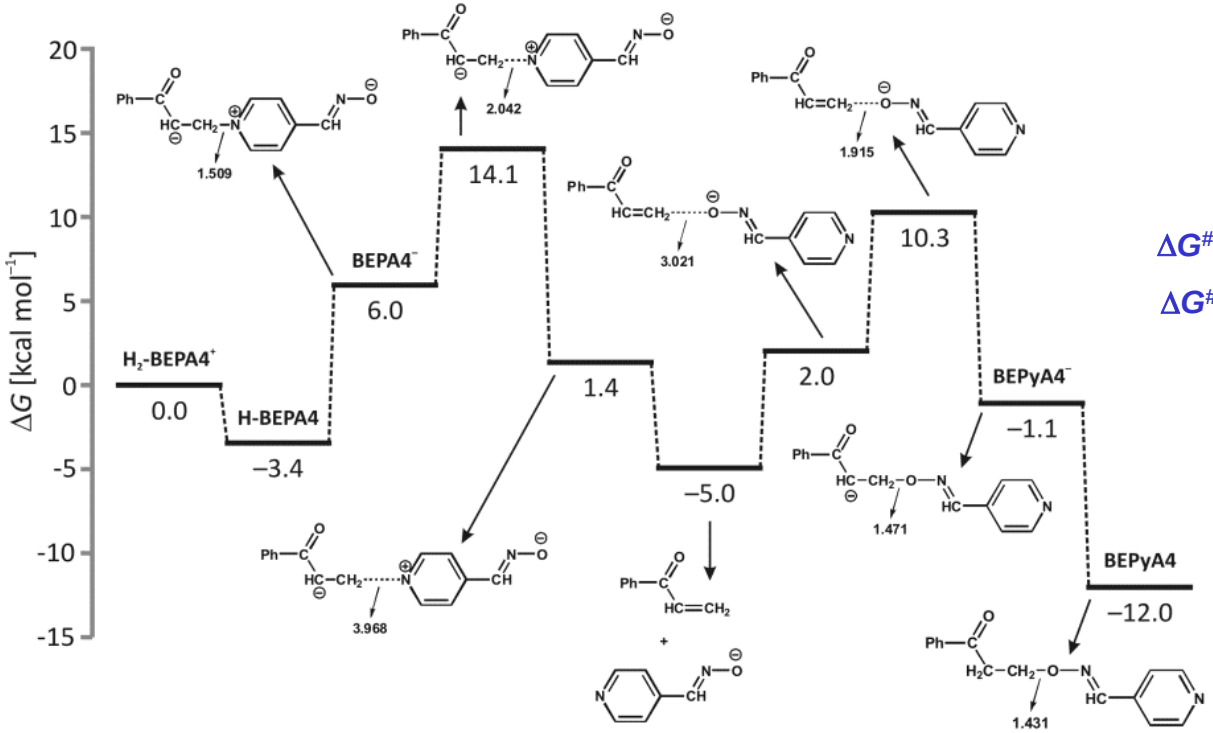
piridin	0 %	**pK_a(piridin / DMF) = 3.6**	**molecule$^-$**	15.2	–7.2
DBU / DMF	9 %	**pK_a(DBU / DMF) = 15.0**	**molecule^{2-}**	13.5	–16.9
K_2CO_3 / DMF	11 %	**pK_a(K_2CO_3 / DMF) = 20.5**	**molecule^{3-}**	9.0	–37.4
***t*Bu-P4 / DMF**	**100 %**	**pK_a(*t*Bu-P4 / DMF) = 42.7**			

Eur. J. Org. Chem. **2015**, *35*, 7695–7704

Mehanizam kemijskih reakcija u organskoj kemiji – pregradnja oksima



N-Benzoylethylpyridinium-4-oximate *O*-Benzoylethylpyridine-4-oxime ether

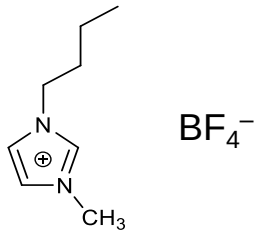


$\Delta G^{\#}$(calc) = 17.5 kcal/mol

$\Delta G^{\#}$(exp) = 18.8 kcal/mol

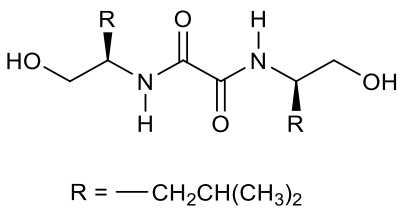
J. Org. Chem. **2015**, *80*, 2165–2173

Dizajn novih materijala – gelovi ionskih tekućina povećanih vodljivosti

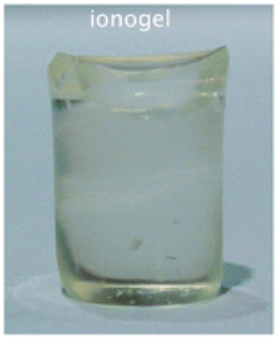


[BMIm] [BF_4]

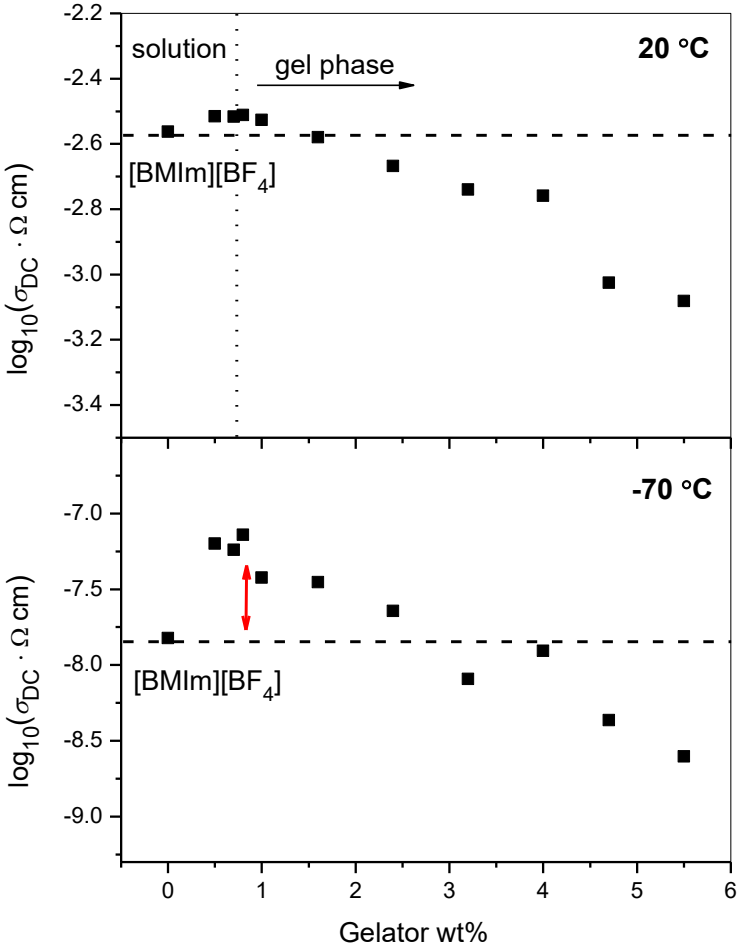
+

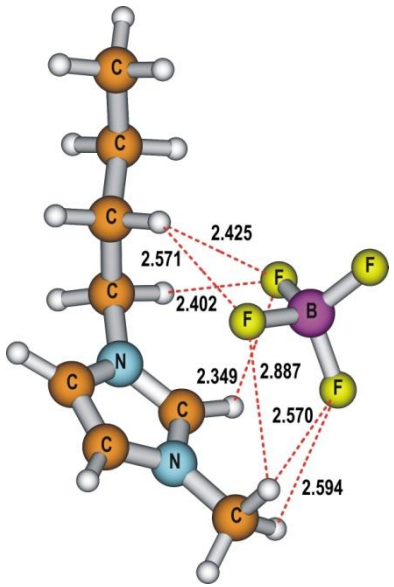


[gelator]



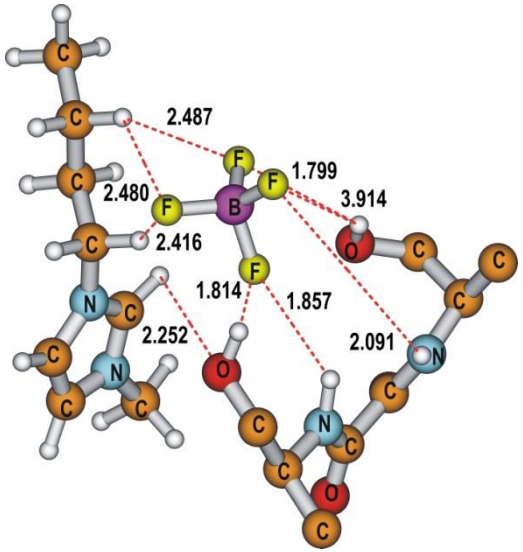
[BMIm] [BF_4] [**gelator**]





[BMIm] [BF_4]

ΔE_{INT} = –92.2 kcal/mol



[BMIm] [BF_4] [**gelator**]

ΔE_{INT} = –116.2 kcal/mol

[BMIm] [BF_4]

ΔE_{INT} = –66.6 kcal/mol

[BMIm] [**gelator**]

ΔE_{INT} = –5.6 kcal/mol

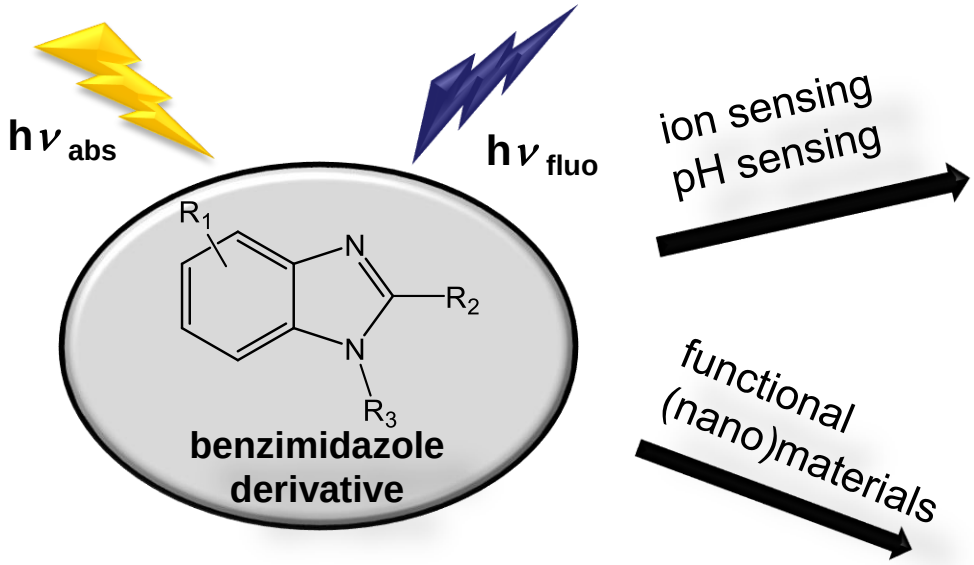
[BF_4] [**gelator**]

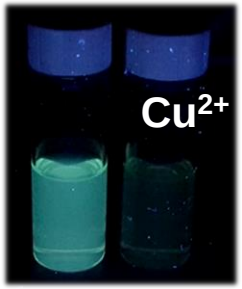
ΔE_{INT} = –20.7 kcal/mol

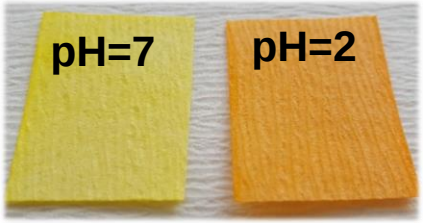
- **Geliranje smanjuje interakciju komponenti ionske tekućine za oko 40%**
- **Molekula gelatora oko 4 puta jače intereagira s anionskom komponentom ionske tekućine**

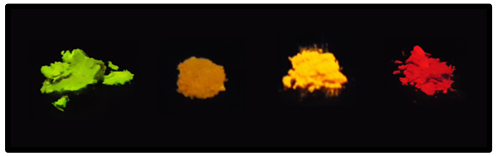
Chem. - Eur. J. **2015**, *21*, 12121–12128

Dizajn novih materijala – kemijski senzori i senzorske molekule









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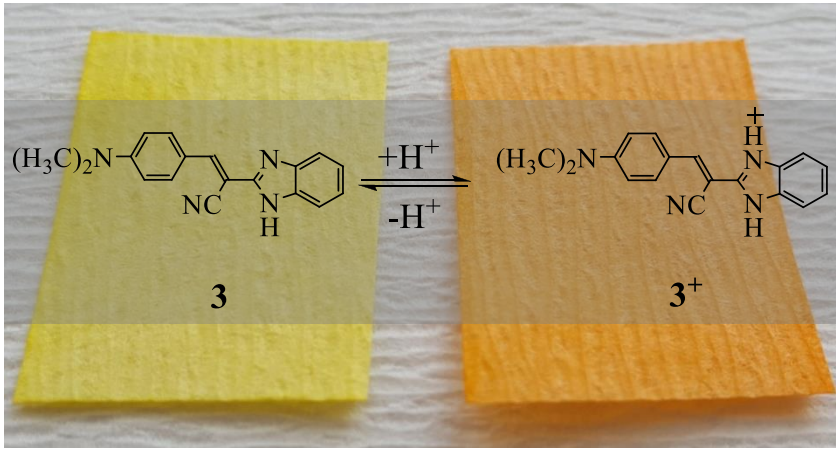
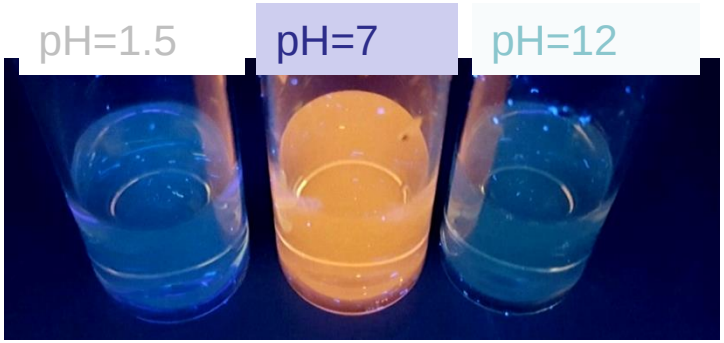
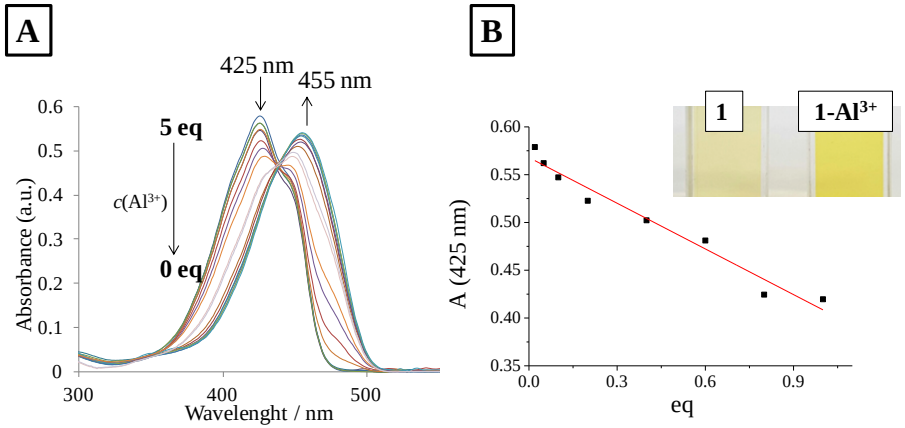
Hrvatska zaklada za znanost
iNFiNiTE–SENS (2015–2019)

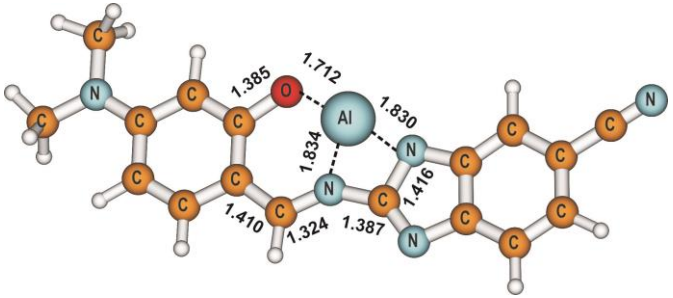
pH senzori



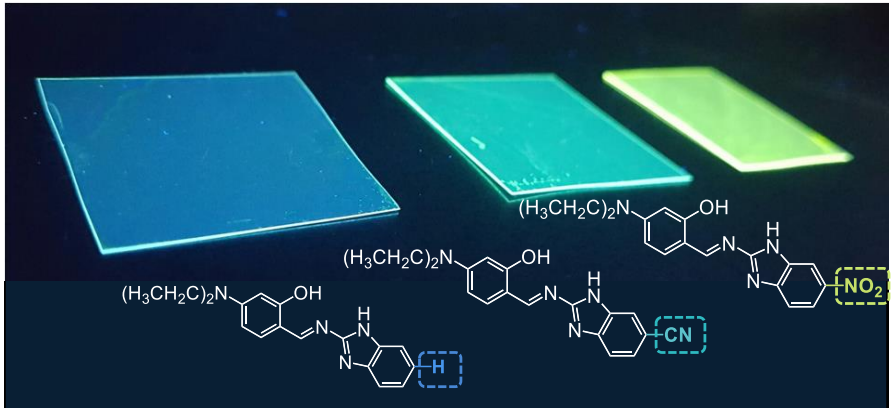


senzori na metalne ione

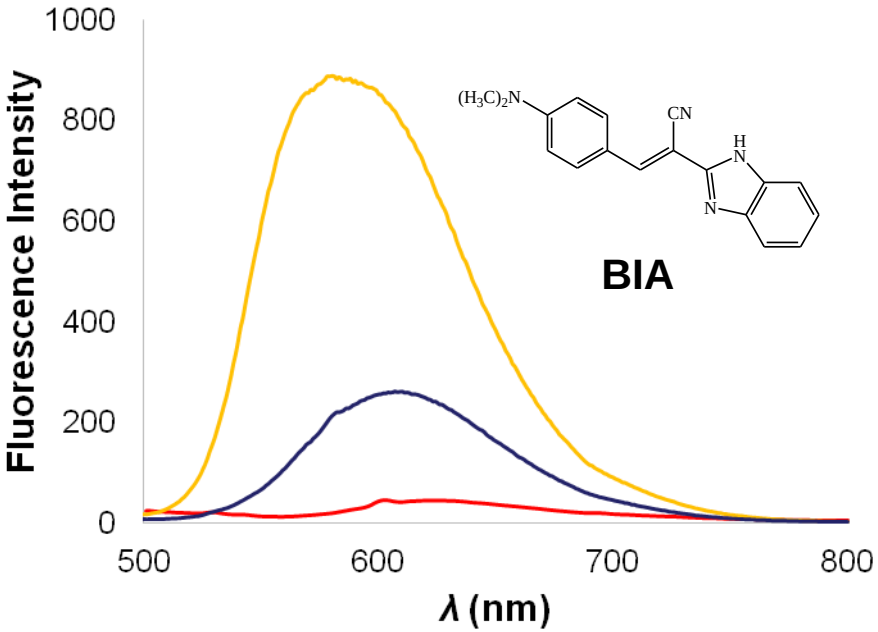


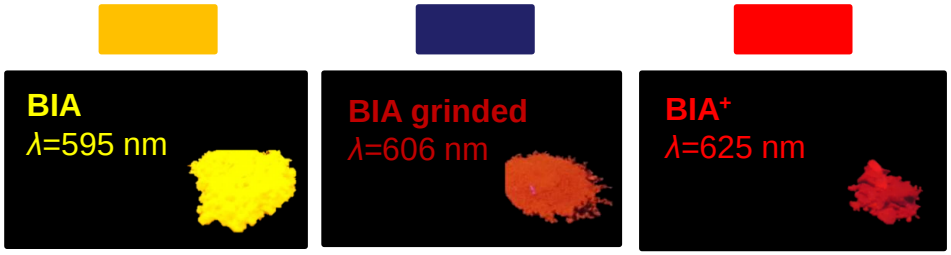


pH osjetljive fluorescentne membrane



senzori osjetljivi na vanjske podražaje





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SEVENTH FRAMEWORK PROGRAMME
MARIE CURIE ACTIONS
HRZZ Croatian Science Foundation
Ministarstvo znanosti i obrazovanja
UNITY THROUGH KNOWLEDGE FUND
APO
ACADEMIA SCIENTIARUM ET ARTIUM CROATICA MDCCCLXI