J.Heyrovský Institute of Physical Chemistry

Collaborations bridging Physics, Chemistry, and Biology: Dreams and Reality

A joint seminar between IOCB and JHIPC

Location: **J. Heyrovský Insitute of Physical Chemistry, Brdička lecture hall,**

Date: **November 13th 2018**

After introductory comments from the Institute's Directors, three pairs of speakers will first talk about the interesting results obtained in recent collaborations between our two institutes, showcasing successful combinations of physical chemistry with organic chemistry and/or biochemistry. Afterwards, several individual scientists will present their current work that may attract the interest of colleagues from the other institute. The potential for further collaborations will finally be explored in a moderated panel discussion.

ÚOCHB AV ČR
IOCB PRAGUE

Ústav fyzikální chemie J.Heyrovského

J.Heyrovský Institute of Physical Chemistry

Time	Speakers	Presentation
9:30-10:00	**M. Hof** Z. Hostomský	Opening; Presentation of both institutes and their research directions, groups facilities, equipment etc
10:00-10:45	**P. Jurkiewicz** P. Jungwirth	Modelling of lipid membranes - simulations and experiments
10:45 -11:00 – COFFEE BREAK		
11:00-11:45	**M. Srnec** L. Rulíšek	From Computational Electrochemistry to Biocatalysis
11:45-12:30	**Petr Kovaříček** P. Cígler	Running Chemistry
12:30-14:00 – LUNCH		
14:00-14:15	**V. Kolivoška**	Charge transport through single molecules
14:15-14:30	I. Starý	Inherently chiral aromatic systems between chemistry and physics
14:30-14:45	**M. Ferus**	Experimental and theoretical exploration of Exoplanetary Atmospheres — Chemistry, Formation Conditions, and Habitability
14:45-15:00	E. Kudová	Neurosteroids with neuroprotective properties *in vivo*: Unmet needs for systematic evaluation of physicochemical properties, 3D structures and behavior in membranes
15:00-15:15	**J. Fedor**	Electron collisions in Physics, Chemistry, and Biology: Reality
15:15-15:45 – COFFEE BREAK		

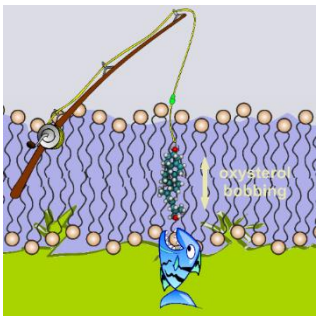
15:45-16:00	**J. Lazar**	Learning about protein structure and function from polarization fluorescence microscopy
16:00-16:15	**E. Pluhařová-Krupičková**	Molecular Modelling of Enzyme Catalysis in Organic Solvents
16:15-16:30	**V. Kašička**	Capillary electrophoresis - powerful tool for physicochemical characterization of (bio)molecules
16:30-16:45	**O. Frank**	Interfacing 2D materials to their environment: stress and charge transfer
16:45-17:00	**J. Kaleta**	How to Convince Molecules to Form Regular 2D Arrays?
17:00-17:20 PANEL DISCUSSION		
DINNER (speakers & directors)		

Please note: Lunch will not be provided, however there are several places in the local area for food (eg. Jidelna Slovanka)

ABSTRACTS:

Piotr Jurkiewicz & Pavel Jungwirth

Modelling of lipid membranes - simulations and experiments



Complexity of lipid membranes calls for sensitive and versatile experimental techniques from one side and powerful yet careful modelling from the other. We know from our experience that fluorescence methods and molecular dynamics benefit from each other. Molecular dynamics provides an interpretation of the experimental results at the atomistic level, while the experiments validate the assumptions made in the simulations. Tuning parameters used in both approaches to match each other as close as possible is trivial yet crucial element of our collaboration.

Dialog between the two fields help us to better understand the other side but also ourselves. The constant challenge of explaining the meaning of our own findings, defining the measured/simulated quantities and setting the limits within which they can be interpreted is a catalyst of science.

We present our attempts to join experimental and computational forces based on 3 examples: 1) adsorption of calcium ions to lipid bilayer, 2) transmembrane movement of the oxidized cholesterol, and 3) discovering a new mechanism of membrane penetration by peptides.

1) Salt ions are omnipresent in physiological fluids, but their interactions with biomolecules are anything but simple. Studying the adsorption of calcium ion to model lipid membranes using Time-Dependent Fluorescence-Shift and Molecular Dynamics simulations reveals part of this complexity. Our results show membrane buffering capacity and the mechanism of the often neglected interactions of calcium ion with lipids. This finding were possible only thanks to the recent development in the methods used, and particularly a new molecular dynamics force-fields.
2) Oxidation of cholesterol in our bodies can be a trigger in cellular signaling, but is also a hallmark of many pathological conditions. Our simulations reveal a special mechanism of the translocation of a tail-oxidized cholesterol, which not unlike a fishing float, oscillates between the two lipid leaflets of a lipid bilayer. This fast movement, which we have called bobbing, serves as an explanation of cholesterol transport and cellular signaling. But, it poses a serious challenge for the experimental techniques, and no direct measurement of this phenomenon is so far possible.
3) The ability of certain peptides to pass cellular membrane and enter a cell is very interesting not only to understand the pathologies that can be activated by this process, but also to develop drugs that could efficiently penetrate target cells. Close collaboration between experimentalists and theoreticians and many hours spent together both at the microscope and at the computer resulted in the discovery of yet another such mechanism. Our results link membrane penetration by peptides to calcium-induced membrane fusion. Wide range of the used technique allowed characterization of the process in terms of membrane curvature calculations, atomistic and coarse-grain simulations, fluorescence studies in model membranes, as well as, electro- and fluorescence- microscopy of the peptides in cell membranes.

In our presentation we focus on the interplay of our theoretical and experimental approaches. We show not only bright sides of the collaboration, but also the pitfalls. We explain how we avoid them and, sometimes, how we fall into them, when trying to fish out the nature of lipid membrane-related processes.

[1] Melcrova et al. (2016) *Scientific Reports* 6:38035; doi: 10.1038/srep38035.
[2] Kulig et al. (2018) *Journal of Physical Chemistry Letters* 9:1118; doi: 10.1021/acs.jpclett.8b00211.
[3] Allolio et al., *Submitted to PNAS*

Lubomír Rulíšek & Martin Srnec

From Computational Electrochemistry to Biocatalysis

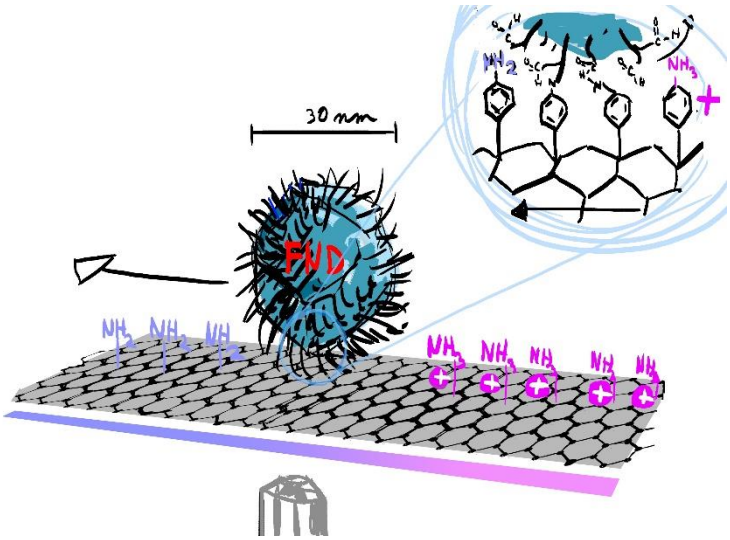
Non-heme iron (NHFe) sites in proteins and their synthetic models are involved in many chemical transformations. Important common theme for these species is that their chemistry is closely related to redox properties, which are in turn determined by many factors that arise from the large variability in oxidation, spin and protonation states, molecular charges, types of ligands, ligand fields, and solvent environments. Here, we discuss perspectives and limits of current quantum chemistry and computational electrochemistry and relate them to reaction mechanisms of non-heme diiron enzymes (Δ^9-desaturase and methane monooxygenase). In particular, we present applications of multi-reference wavefunction methods to bioinorganic systems, such as NHFe together with the methodology for calculation of reduction potentials ($E°$) along with its application to very challenging ferryl ($Fe^{IV}O$) species and we provide direct connection of their redox chemistry to a relevant field of biomimetic NHFe catalysis. Importantly, we reveal that, beyond a classical thermodynamic effect on kinetics of hydrogen-atom abstraction reactions, there also exist a significant contribution arising from a factor reflecting propensity for (a)synchronicity in concerted H^+/e^- transfers, which stems directly from the reduction potentials and acidity constants of reactants and products.

Petr Kovaříček & Petr Cígler

Running chemistry

Manipulating nanoscopic objects by external stimuli is the cornerstone of nanoscience. Our collaborative research is focused on implementation of dynamic covalent chemistry to directional motion of nanoparticles. Two main components of the research will be presented: construction of fluorescent nanoparticles with precisely defined interface and principles of the dynamic covalent chemistry. Recently, we succeeded in opening a pathway for thermodynamically controlled manipulation of objects on the nanoscale [1]. We will discuss our system enabling the reversible binding and directional motion of fluorescent nanodiamond particles at a functionalized graphene surface via imine linkages. The dynamic connections allow for controlling the formation and rupture of these linkages by external stimuli. By introduction of pH gradients, the nanoparticles are driven to move along the gradient due to the different rates of the imine condensation and hydrolysis in the two environments. The multivalent nature of the particle-to-surface connection ensures that particles remain attached to the surface, whereas its dynamic character allows for exchange reaction, thus leading to displacement yet bound behavior in two-dimensional space. We will also discuss new, currently investigated approaches enabling multidirectional controlled motion of nanoparticles. These involve construction of nanoparticle hybrids consisting of fluorescent nanodiamonds and magnetic nanoparticles. The utilized driving forces are concentration gradient and magnetic field.

[1] Kovaricek et al., *ACS Nano* **2018**, *12*, 7141−7147.



Viliam Kolivoška

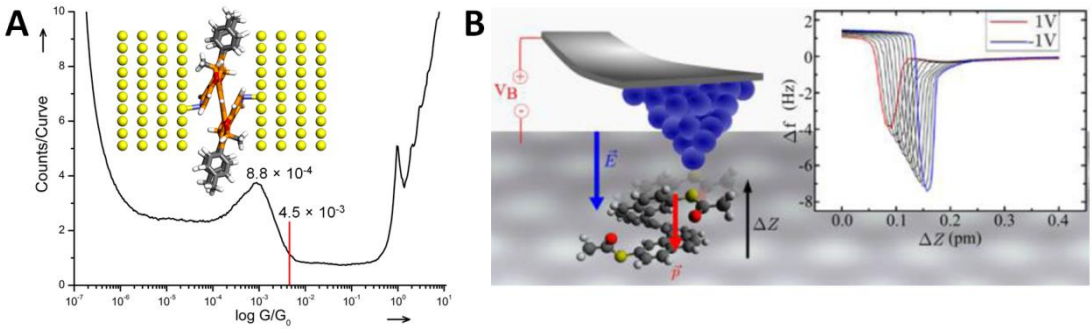
Charge transport through single molecules

Molecular electronics is a field of nanotechnology aimed at building functional electronic circuits composed of elements based on single molecules as an alternative to currently used silicon based technologies. The charge transport (electric conductance) in individual molecules is governed by their electronic structure and may be experimentally inspected in a metal-single molecule-metal junction subjected to mechanical elongation forming the basis of break junction techniques. In this work, we use scanning tunneling microscopy break junction technique as an experimental platform to investigate charge transport in selected series of molecular electronic components, looking for structure-property relationships and transport pathways in particular molecular junction configurations. We particularly address the role of length, anchoring groups and conjugation pattern of the molecule. Results obtained by the experimental break junction technique are further complemented by theoretical charge transport calculations based on the combination of density functional theory and non-equilibrium Green function formalism.

Ivo Starý

Inherently chiral aromatic systems between chemistry and physics

The preparation of nontrivial helically chiral aromatics and exploration of their physico-chemical properties attract a considerable attention these days. Hand in hand with the development of their synthesis, an increasing number of applications to chemistry, physics and biology has been described in the literature. Relying on the robust [2+2+2] alkyne cycloisomerisation, we have demonstrated the successful synthesis of a wide range of helically chiral (hetero)helicenes encompassing functionalised, laterally/axially extended and enantiopure derivatives. However, we are interested also in particular chemical and physical properties of functionalised (hetero)helicenes such as single-molecule conductivity,[1] piezoelectric behaviour[2] or their on-surface chemistry.[3]



A: Experimental and calculated single-molecule conductance of a helicene derivative (measured by the MC/STM break junction method); B: UHV AFM experiment demonstrating a single-molecule converse piezoelectric effect at a helicene derivative.

[1] Nejedlý, J.; Šámal, M.; Rybáček, J.; Tobrmanová, M.; Szydlo, F.; Coudret, C.; Neumeier, M.; Vacek, J.; Vacek Chocholoušová, J.; Buděšínský, M.; Šaman, D.; Bednárová, L.; Sieger, L.; Stará, I. G.; Starý, I. *Angew. Chem. Int. Ed*. **2017**, *56*, 5839–5843.

[2] Stetsovych, O.; Mutombo, P.; Švec, M.; Šámal, M.; Nejedlý, J.; Císařová, I.; Vázquez, H.; Moro-Lagares, M.; Berger, J.; Vacek, J.; Stará, I. G.; Starý, I.; Jelínek, P. *J. Am. Chem. Soc*. **2018**, *140*, 940–946.

[3] Stetsovych, O.; Švec, M.; Vacek, J.; Chocholoušová, J. V.; Jančařík, A.; Rybáček, J.; Kosmider, K.; Stará, I. G.; Jelínek, P.; Starý, I. *Nat. Chem.* **2017**, *9*, 213–218.

J.Heyrovský Institute of Physical Chemistry

Martin Ferus

Experimental and theoretical exploration of Exoplanetary Atmospheres — Chemistry, Formation Conditions, and Habitability

Our current research is focused on various physical and chemical processes occurring in atmospheres of exoplanets exposed to intense extreme ultraviolet radiation emitted by young stars located in the center of their planetary systems and plasmas created by high-velocity impacts of extraplanetary bodies and atmospheric electrical discharges of a different kind. The explorations are performed using advanced facilities, devices, diagnostics and experimental layouts combined with the theory and computer simulations, chemical consequences of particular processes (e.g., shock, thermal and blast waves, non-thermal action of energetic photons and charged particles, fast quenching of the hot plasmas by ambient cold gas and surfaces of condensed matter, and so on) associated with the above-mentioned high-energy density events in the atmospheres, especially that on young exoplanets. These results make it possible to achieve a more reliable interpretation of observation astronomy data, to simulate the transmission spectra and to estimate chemical conditions of prebiotic synthesis on young planets.

Eva Kudová

Neurosteroids with neuroprotective properties *in vivo*: Unmet needs for systematic evaluation of physicochemical properties, 3D structures and behavior in membranes

Neurosteroids developed at the department of Steroidal Inhibitors have been originally developed as inhibitors of N-methyl-D-aspartate receptors. These compounds have been demonstrated as neuroprotectives in several models of CNS-indications (epilepsy, neuropathic pain, ischemie,etc.). The sicky issue about steroids is how neurosteroids target receptor function. The interactions of neurosteroids with NMDAR constitute a complicated process. It was suggested that neurosteroids form micelles occurring in the extracellular liquid which can fuse with the membrane; next single steroid molecules leave the membrane and enter into the channel vestibule, which is the hydrophobic site of action. The inhibitors interact with the non-polar NMDAR channel mostly through attractive van der Waals interactions which compete with repulsive effects such as dessolvation and repulsion due to the presence of charged and polar groups in neurosteroids. The kinetics of neurosteroid binding and inhibition is slow and not typical of a simple receptor-ligand interaction in an aqueous solution. This indirectly suggests the importance of the plasma membrane as a compartment where the steroid accumulates to reach its site of action on NMDARs. Evaluation of physicochemical properties, 3D structures and their behavior in membranes of biologically active vs. inactive neurosteroids from our laboratory may clarify their mechanism of action and lead to practical outcomes in the design of new neurosteroids analogues.

Juraj Fedor

Electron collisions in physics, chemistry and biology: reality

I will provide a brief overview of the electron collision laboratory at the Heyrovský Institute. We are equipped with three dedicated setups to measure cross sections for various scattering channels of free electrons on gas-phase targets. We specialize on properties of resonances – temporary anion states – created in these collisions.

Motivation for our work comes from several directions.

Fundamental research: molecular dissociation via resonances is accompanied by a strong coupling of electronic and nuclear motion. The non-adiabatic and non-local phenomena, e.g. mixing of states with different symmetries in polar targets [1], leave their imprints in the cross sections. We provide reference data for theoretical models describing processes in scattering continuum.

High-voltage insulation technology: The electron collisions play a key role in the inception (via ionization avalanche) and the prevention (via electron attachment) of the electric breakdown of gases. Within an industrial collaboration, we quantitatively probe these processes in the potential replacement gases for SF_6 in in the high-voltage switchgear.

Radiation damage: The secondary electrons created when high-energy radiation passes the biological tissue, efficiently dissociate the biomolecules via formation of the resonances. We investigate the mechanism of this dissociation in the suitable model systems, e.g. microhydrated nucleobases [2].

[1] M. Zawadzki et al., Phys. Rev. Lett. 121 (2018) 143402

[2] J. Kočišek et al, J. Phys. Chem. Lett. 7 (2016) 3401

J.Heyrovský Institute of Physical Chemistry

Josef Lazar

Learning about protein structure and function from polarization fluorescence microscopy

Fluorescence, with its various aspects, can serve as a rich source of information about molecular structure and environment. In order to learn about various molecular events taking place in living cells and organisms, we have resorted to techniques of polarization fluorescence microscopy. Our work shows that two-photon polarization microscopy (2PPM) is a powerful technique allowing observations of molecular processes, yielding insights into protein structure, and enabling rational development of genetically encoded optical probes.

J.Heyrovský Institute of Physical Chemistry

Eva Pluhařová-Krupičková

Molecular Modelling of Enzyme Catalysis in Organic Solvents

Enzymes are extraordinary catalysts satisfying the needs of living organisms, but their efficiency and selectivity is also appealing for utilizing them in technological applications [1]. However, their natural aqueous environment is a poor medium for most synthetic transformations mainly because of the low substrate solubility and side reactions involving water. Perhaps surprisingly, a wide range of enzymes do not denature and moreover retain catalytic activity in organic solvents. This opens a path for carrying out new unnatural reactions. The change of reaction medium significantly alters enzyme activity, as well as chemo-, regio- and enantioselectivity, as is demonstrated, for example by decrease of reaction rates by 10^3 - 10^5 times or reversal of enantioselectivity [2]. The strategies for tuning and improving enzymatic function in organic media are not limited only to protein mutations, but also optimizing the composition of the reaction medium. To be able to predict the outcome of protein and medium engineering, we need a molecular level insight which can be provided by various methods of theoretical chemistry.

Our first example is the atomistic simulation of activation of Subtilsin Carlsberg in hexane by traces of water. We will show that instead of traditional explanation of the effect of water involving changes of the protein flexibility or polarity in the active site, conformational equilibrium of the bound substrate significantly affects the catalytic rate constant. Next, we will discuss the puzzling non-monotonic dependence of enantioselectivity of a transesterification reaction catalyzed by Candida antarctica lipase B on solvent properties.

[1] A. M. Klibanov, *Nature* **409**, 241 (2001).
[2] S. Tawaki, A. M. Klibanov, *J. Am. Chem. Soc.* **114**, 1882 (1992).

J.Heyrovský Institute of Physical Chemistry

Václav Kašička

Capillary electrophoresis – powerful tool for physicochemical characterization of (bio)molecules

Capillary electrophoresis and other high-performance capillary electromigration (HPCE) methods will be presented as powerful tools for determination of important physicochemical parameters of a wide spectrum of low-, medium- and high-molecular-mass ionogenic compounds. Using the different HPCE methods (zone electrophoresis in free solutions or in sieving/gel media, isotachophoresis, isoelectric focusing, affinity electrophoresis, electrokinetic chromatography, and electrochromatography), the following physicochemical characteristics of (bio)molecules can be determined: effective, ionic and limiting mobilities, effective charges, isoelectric points, Stokes radii, relative molecular masses, partition coefficients, diffusion coefficients, and acidity (ionization) constants (pK_a) of their ionogenic groups. In addition, the binding (stability, association, formation, or dissociation) constants of (bio)molecular complexes and rate constants of chemical reactions, enzymatic conversions, and noncovalent molecular interactions can be estimated. Advantages of HPCE methods for these physicochemical measurements include high separation efficiency, short analysis time, and especially high sensitivity – typically, picomole substance amounts in nanolitre volume are injected for single analysis. Moreover, the characterization of not quite pure and not quite stable solutes and solutes sparingly soluble in water is possible.

[1] Štěpánová S., Kašička V.: Application of capillary electromigration methods for physico-chemical measurements, in Poole C. (Ed.): Capillary Electromigration Separation Methods, Elsevier, Amsterdam, 2018, pp. 547-591.

[2] Geffertová G., Ali S.T., Šolínová V., Krečmerová M., Holý A., Havlas Z., Kašička V.: Investigation of the acid-base and electromigration properties of 5-azacytosine derivatives using capillary electrophoresis and density functional theory calculations, Journal of Chromatography A 2017, 1479, 185-193.

[3] Tůmová T., Monincová L., Nešuta O., Čeřovský V., Kašička V.: Determination of effective charges and ionic mobilities of polycationic antimicrobial peptides by capillary isotacho-phoresis and capillary zone electrophoresis. Electrophoresis 2017, 38, 2018-2024.

Otakar Frank

Interfacing 2D materials to their environment: stress and charge transfer

The properties of 2D materials (2DM), however unique, are substantially influenced by their immediate environment. Molecules in the surrounding atmosphere as well as atoms in the substrate transfer charge to 2DM. The charge carriers from the environment – even molecules from air - induce substantial change in the density of states and Fermi level. This phenomenon can take place not only globally – being the reason for graphene so promising in, e.g., sensing applications, but also locally, where differently charged atoms in the substrate promote the formation of inhomogeneities in carrier concentration and thereby considerable scattering in the 2DM. A similar effect can be generated by local deformation singularities due to substrate roughness. The extreme susceptibility to the ambience can be a bottleneck as well as a great opportunity to further boost the applicability of these unique materials. Indeed, the highest Young's modulus and strength of graphene together with low bending rigidity provide ample opportunities to tune its electronic structure by deformation, both unwanted (as mentioned above) and desired, the so-called "strain engineering". In bilayer graphene, inhomogeneous in-plane strain could even lead to band gap opening and out-of-plane compression is able to tweak the optical transitions when the layers are misoriented [1]. Out-of-plane compression is also able to strongly modify the electronic structure of transition metal dichalcogenides [2]. While ordered arrays of topographical corrugations might provide the desired uniform deformation fields, their long-range control is still an issue. Possible routes towards this task have been recently hinted: through specific thermal treatment of uncured underlying polymer for fully supported wrinkles, or through linear defects in self-supported graphene membranes on nano-pillar arrays [3].

[1] E. del Corro, M. Peña-Alvarez, K. Sato, A. Morales-Garcia, M. Bousa, M. Mračko, R. Kolman, B. Pacakova, L. Kavan, M. Kalbac, and O. Frank, *Physical Review B* **95**, 085138 (2017).
[2] M. Peña-Álvarez, E. del Corro, Á. Morales-García, L. Kavan, M. Kalbac, and O. Frank, *Nano Letters* **15**, 3139 (2015).
[3] B. Pacakova, T. Verhagen, M. Bousa, U. Hübner, J. Vejpravova, M. Kalbac, and O. Frank, *Scientific Reports* **7**, 10003 (2017).

Jiří Kaleta

How to Convince Molecules to Form Regular 2D Arrays?

Two different approaches towards two-dimensional arrays of molecular-level devices like dipolar rotors, motors, and switches will be presented. It is expected that regular arrangement of such objects will lead to amplification of their properties. Molecules of the Type A (Figure 1) were designed [1] to form surface inclusions on a facets of porous zeolite-like crystalline material called tris(*o*-phenylenedioxy)cyclotriphospazene (usually abbreviated as TPP). These rod-like molecules consist of several crucial units: (a) bicyclo[1.1.1]pentane-based tail that has high affinity towards TPP channels and helps to anchor molecular machine on a surface of TPP crystal, (b) bulky triptycene prevents complete insertion into the matrix and (c) functional unit (unidirectional light-driven molecular motor is depicted). [2] The triptycene moieties of the rod-shaped molecules of the Type B (Figure 1) carrying an axial rotator are designed to interleave on an aqueous surface into Langmuir-Blodgett (LB) monolayers containing a two dimensional trigonal array of dipoles rotatable about an axis normal to the surface. Monolayer formation and its exact structure were verified by in situ grazing incidence X-ray diffraction directly on the aqueous surface. [3] LB films transferred to gold substrates were studied by ellipsometry, infrared spectroscopy, and photoelectron spectroscopy.

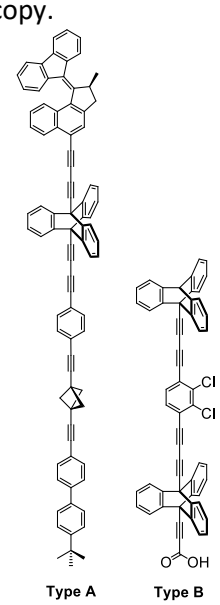


Figure 1. Structures of selected molecular-level devices.

[1] Kaleta, J.; Dron, P. I.; Zhao, K.; Shen, Y.; Císařová, I.; Rogers, C. T.; Michl, J. J. Org. Chem. 2015, 80, 6173-6192.

[2] Kaleta, J.; Chen, J.; Bastien, G.; Dračínský, M.; Mašát, M.; Rogers, C. T.; Feringa, B. L.; Michl, J. J.Am. Chem. Soc. 2017, 139, 10486-10498.

[3] Kaleta, J.; Wen, J.; Magnera, T. F.; Dron, P. I.; Zhu, C.; Michl, J. PNAS 2018, DOI:10.1073/pnas.1712789115.