Inquiries: valentin.koehler@unibas.ch, Tel: +41 (0)61 267 10 09
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Tailor-Made Proteins and Peptides for Quantum Interference Experiments

(PI: Valentin Köhler, Department of Chemistry, University of Basel; Co-PI and faculty member: Marcel Mayor, Department of Chemistry, University of Basel)

In recent years synthetic chemistry and quantum optics have teamed up with three major objectives in mind and are now in an encouraging position for the inclusion of molecular biology: 1st: we face the open research challenge to test the linearity of quantum mechanics in the regime of high masses - and with it the concepts of quantum delocalization, quantum superposition and matter-wave interference. The mass world record in matter-wave interference is currently held by a consortium between the synthetic chemistry group in Basel and the experimental quantum nanophysics group in Vienna.[1] 2nd: the same teams have pioneered a new approach to quantum-assisted molecule metrology. Matter-wave interferometry creates refined molecular nanopatterns that are sensitive to external fields and can be used to retrieve internal molecular properties in the presence of known forces. In the past, this has allowed us to determine molecular polarizabilities,[2] vibrationally induced dipole moments,[3] molecular fragmentation[4] or to distinguish structural isomers.[5] 3rd: by carefully tailoring the molecular properties we were able to demonstrate the evolution of the diffraction pattern molecule by molecule and thus to unambiguously demonstrate the wave nature of the moving molecular particle.[6]

Most recently, we have been intrigued by the question to what extent it may be possible to translate these achievements with tailor-made molecules into the world of biomolecular physics. Quantum experiments are expected to be compatible with neutral biomolecular beams that stay beyond a momentum of p=30.000 amu×30m/s. This covers the mass of insulin, cytochrome c, calmodulin and GFP in the given velocity range or even more massive proteins such as hemoglobin (64 kDa), or cryptochrome at lower speed. Substantially bigger complexes, such as ferritin (~900 kDa) are interesting for optical and magnetic manipulation experiments,[7] in particular with appropriate functionalization (see below).

A key challenge is to generate a beam of slow, directed, velocity and mass-selected biomolecules in high vacuum. Peripheral chemical functionalization with perfluoroalkyl chains[8] has proven to facilitate the promotion of intact massive molecules via thermal and laser assisted desorption methods.[9] In this interdisciplinary approach between synthetic chemistry and bio-engineering, we propose the stepwise development of amino-acid based biomolecules for interference experiments. While the design and synthesis of these model compounds is based within the SNI at the University of Basel, the investigation of their physical properties is performed in close cooperation with the group of Markus Arndt at the University of Vienna. We enjoy a close, long standing and fruitful collaboration to address such interdisciplinary challenges. His group is very interested in suitably functionalized biomolecules and is performing both preliminary volatilization studies and, as soon as biomolecules with suitable properties are available, also interference experiments as project partner without financial support by the SNI.

With the final goal of proving the wave nature of proteins, the initial challenges are mainly of chemical and biochemical nature and thus the support of synthetic chemistry and bio-engineering by the SNI would launch a timely high risk - high reward project. In particular we aim at the stepwise development of biomolecules with increasing size for interference experiments. Starting with small peptides, their volatilization (suitability for slow

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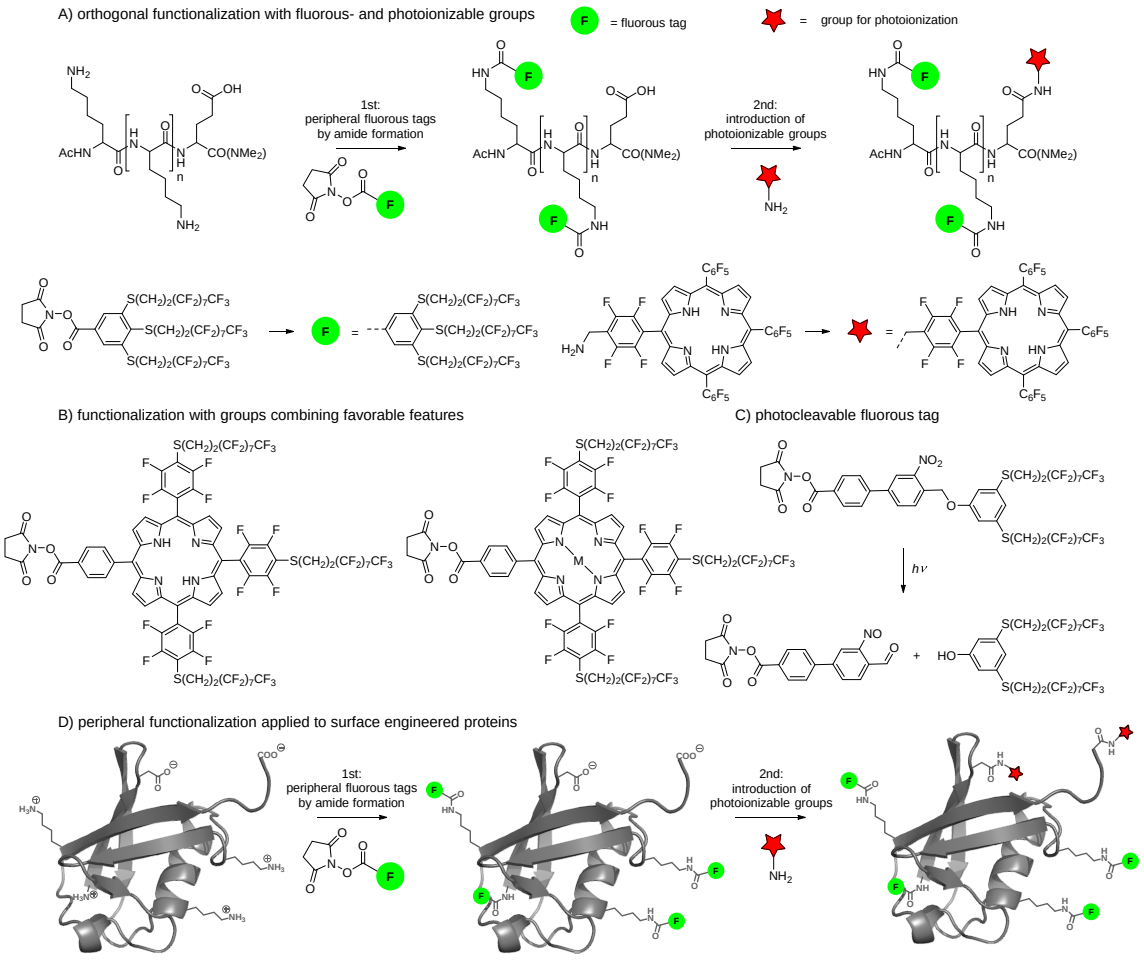
molecular beam formation) and ionization (detection after scattering) features shall be optimized. Profiting from these small bio-oligomers as proxy, we subsequently apply the design principles to bio-polymers of increasing size and hope to be able to push the mass limit up to suitably functionalized proteins.

The sublimability of molecules is increased by reducing their intermolecular interactions and thus, peptides exposing fluorinated groups are at the focus of interest. As a starting point, lysine rich model peptides were selected for the decoration with fluorous tags. The exposed primary amino group of lysine is ideally suited for post-functionalization. [10] As displayed below, suitable electrophiles (e.g. NHS esters) enable the peripheral functionalization with groups exposing fluorous alkyl chains. The complementary conversion of carboxylic residues[10] displayed in A) further permits the introduction of a photo-ionizable label to facilitate the peptide's detection by mass spectrometry. Initially we would like to investigate the number of peripheral perfluorinated alkyl groups required for the volatilization of model peptides. The modular assembly of peptides is ideally suited to study the correlation between their molecular mass and number of fluorous chains required. The features introduced by the tag can also be combined as exemplified in the photo-ionizable porphyrin tag exposing long perfluorinated alkyl chains (displayed in B). Of particular interest are photo-cleavable tags (see C) which enable future interference experiments based on optical gratings. The developed technology will subsequently be adapted to surface engineered proteins (see D). Heterologous expression in *E. coli* allows control of surface residue composition by technically facile site directed mutagenesis. The outlined bio-chemical approach of protein modification also enables the global manipulation of surface charges, a particular important feature as only neutral bio-molecules are suited for interference experiments. To what extent these manipulations will interfere with the folding of the protein core will be subject of the here performed investigations. [11,12]



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