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Abstracts

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Transmembrane Transport: Simulation-Guided Discovery

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Transmembrane transport underpins numerous biological functions and offers opportunities for biotechnology, therapeutics, and nanofluidic engineering. This talk brings together two simulation-led approaches applied to transmembrane transport. The first study focuses on the discovery of pore-forming peptides (PFPs) that disrupt lipid bilayers. Identifying short PFPs is challenging since most are similar in length to the thickness of the bilayer (~22 amino acids). Here we employed an active machine learning strategy (directed by coarse-grain molecular dynamics simulations) to navigate the vast octapeptide sequence-space and prioritise candidate peptides. From 25.6 billion possible sequences, 71 potential membrane-active candidates were identified. 13 were verified experimentally, with one forming particularly stable discrete pores. In addition, the sequence characteristics associated with membrane-disrupting behaviour were revealed. The second study used atomistic molecular dynamics simulations to investigate the possibility of constructing a nanoscale Archimedes screw pump from a rapidly rotating DNA helix within a nanopore. At MHz rotational speeds, water and ions were driven in the same direction regardless of the charge of the DNA or nanopore, consistent with nanoscale screw-pump activity. Electrostatic interactions governed ion selectivity, and preferential transport resulted in electric current generation. Together, these studies show how machine learning and molecular dynamics simulation can be used to identify and design promising systems, define mechanistic limits, and direct future experimental studies.

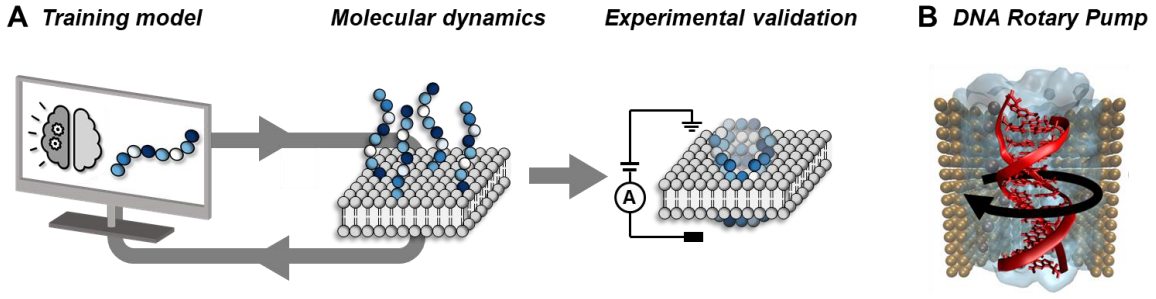

Figure. A) Machine-Learning / atomistic MD simulations guide the discovery of membrane-active peptides. B) Atomistic simulation of a rapidly rotating DNA helix within a nanopore, reveals pumping of water and selective ion transport, resulting in an ion current.

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Polyoxometalate-Based Memory Devices and Computational Chemistry

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Polyoxometalates (POMs) are molecular metal oxides with exceptional redox and electron-storage properties, making them attractive building blocks for molecular electronics.[1] Our work combines device fabrication, electronic structure calculations, and materials modelling to understand and control charge transport in POM-based systems. Previous studies have investigated the role of contact geometry and counterions in molecular junctions,[2] and explored the influence of POMs on semiconductor nanowire behaviour. Recent computational studies further address the impact of counter-cations and solvent environments on electronic properties under realistic conditions. [3] Together, these studies provide insight into the design of functional molecular metal-oxide materials, highlighting both what is known and what remains to be understood. We highlight the limitations of current computational approaches and identify key opportunities for the future design and modelling of functional molecular metal-oxide materials.[4]

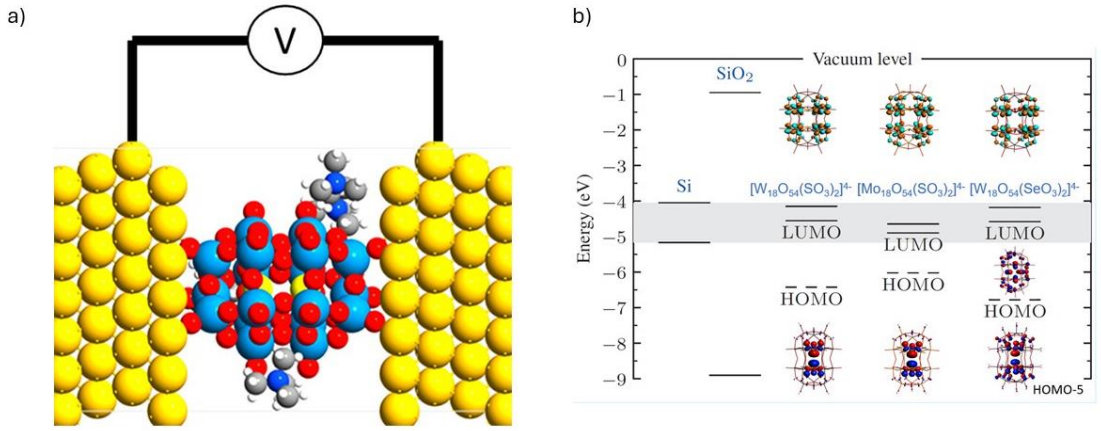

Figure. a) Ideal representation of a molecular metal oxide or polyoxometalate (POM), to study its transport properties of $[W_{18}O_{54}(SO_3)_2]^{4-}$, a POM cluster, in a variety of molecular junction configurations. b) Frontier orbitals energies of $[M_{18}O_{54}(XO_3)_2]^{4-}$ (M= W and Mo, and X=Se and S) compounds and HOMO-LUMO gaps.

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Machine Learning for Supramolecular Design

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Keywords: Machine Learning, Property Prediction, Rational Design

The rise of functional smart materials is transforming modern technology, yet their increasing complexity demands materials with enhanced, tuneable functionality.[1] Many existing smart materials rely on non-renewable, biologically-incompatible metal systems.[2] In contrast, materials formed through the hierarchical assembly of organic small molecules can offer a renewable, bio-compatible alternatives with promising functional versatility. Enabling predictive design of such materials could accelerate the development of sustainable alternatives to metal-based systems in applications ranging from optoelectronic materials to biomedical devices.[3]

While the tunability of these systems offers significant advantages, self-assembling small molecule systems lack guiding design principles as it is difficult to predict how supramolecular interactions at the molecular level affect the bulk material properties.[1] To address this, we explore how quantitative structure-property relationships (QSPR) — models predicting properties from descriptors of chemical structure, predominantly used in drug discovery — can be repurposed to inform the design of functional materials (Figure 1).

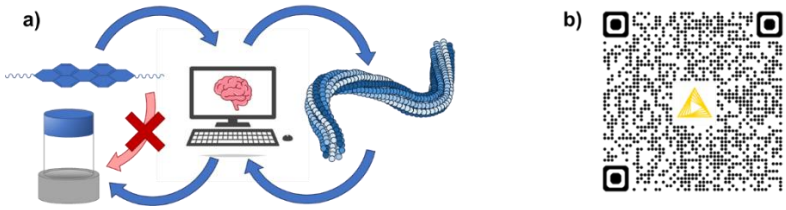

Figure 1 a) Cartoon depicting the application of machine learning predictions of properties in hierarchical assemblies. Structure alone does not identify bulk properties, but the presence of aggregates can be predicted with machine learning, further informing predictions of bulk properties. b) QR code to our open-source classification QSPR.[4]

Our open-source QSPR framework demonstrates predictive power across diverse classification tasks, including molecular solubility and mesoscale micelle formation, underscoring its potential as a generalisable tool for materials discovery.[4] Our approach lays the groundwork for a more systematic, data-driven methodology in materials chemistry, bridging the gap between molecular design and macroscopic function. However, the scarcity of robust, reproducible datasets in materials chemistry remains a major bottleneck. We advocate for standardised characterisation protocols across the field to enable the development of more sophisticated, data-driven design strategies.

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A Multireference Excited State Database for Correlation-Aware Screening of Organic Semiconductors in Excitonic Energy-Materials Discovery

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Accurate prediction of excited-state energetics is essential for the rational design of organic semiconductors that enable next-generation optoelectronic technologies.[1] It is also a prerequisite for reliable machine-learning workflows, which depend on high-quality reference data to learn physically meaningful structure–property relationships.[2] Yet widely used single-reference methods, most notably TD-DFT, can break down for precisely the systems of greatest chemical and technological interest. These include molecules with pronounced static correlation and those exhibiting inverted singlet–triplet gaps (INVEST),[3] a key target property for high-efficiency OLED emitters and emerging photovoltaic concepts.[4]

We introduce the first multireference benchmark dataset tailored to small-molecule organic semiconductors. The collection comprises 1,500 chemically diverse π-conjugated compounds with systematically computed vertical excitation energies for S_1, S_2, T_1, and T_2, together with oscillator strengths for the lowest singlet transitions f_1 and f_2. All values are generated using a consistent multiconfigurational protocol based on state-averaged CASSCF and dynamical correlation via strongly contracted NEVPT2, providing a robust open-access reference for assessing excited-state methodologies on realistic materials motifs.

Beyond the dataset itself, we statistically interrogate method-dependent errors across the full dataset to assess the overall reliability of lower-cost single-reference approaches. We then extend this analysis to individual structural families, identifying cases where lower theory levels may remain sufficient even when dataset-wide trends indicate that multireference treatments are required. This provides practical guidance on when single-reference methods are dependable, when multireference descriptions become necessary, and which molecular families are most sensitive to the chosen level of theory.

Finally, we demonstrate the utility of the benchmark for materials discovery by screening for OLED-relevant INVEST, TADF, and anti-Kasha candidates. Strikingly, INVEST candidates are only identified at the NEVPT2 level, with all 21 molecules missed by both TD-DFT and CASSCF alone. For TADF and anti-Kasha screening, lower-cost methods recover some candidates, but 55 TADF and 82 anti-Kasha candidates remain NEVPT2-exclusive. These results show that dynamical correlation is indispensable for inverted-gap emitters and remains essential for reliable excited-state materials screening more broadly.

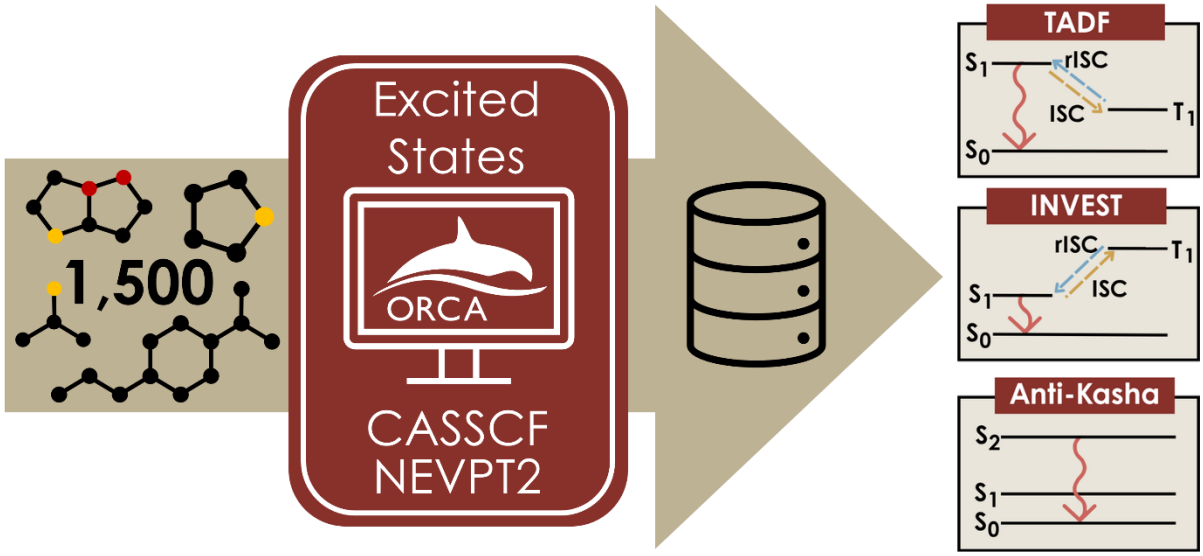

Figure. Graphical abstract

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Peptides at the Interface – A Study on TIP4P Water Models

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The water-ice interface is central to a range of biological and environmental phenomena, including the activity of antifreeze peptides and proteins. Molecular dynamics simulations provide atomistic resolution of interfacial structure and dynamics, but the validity of such simulations is heavily dependent on the choice of water model. Commonly used four-site water models differ substantially in their predicted ice Ih melting temperature,[1] with direct consequences for the thermodynamic accuracy of ice-water interface studies. Here we present a systematic MD simulation study of the water/ice interface using all three models within the CHARMM36M force field with a view of studying the anti-freeze qualities of selected peptide sequences.

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Computational Explorations of Halogenase Substrate Scope

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Cyanophage viruses disrupt photosynthesis in oceanic cyanobacteria by altering the bioactivity of aromatic molecules in the host through halogenation reactions. The VirX1 enzyme facilitates these reactions: beyond its environmental role, it offers a biotechnological route to the regioselective halogenation of a range of aromatic substrates, avoiding harmful reagents.[1,2] While it has historically been understood that only activated aromatics can be halogenated enzymatically, a recent study indicates that unactivated aromatics may be also.[3]

We investigate the substrate scope of VirX1 with respect to activated and unactivated aromatics, beginning with a study of tryptophan, phenylalanine, and benzene. Using docking and molecular dynamics simulations, we equilibrate the enzyme-substrate system and sample conformational space. These sampled structures are then used as starting points for hybrid quantum mechanical/molecular mechanical (QM/MM) calculations (at the M06-2X/def2-QZVP//xTB level)[4,5] which enable us to build reaction energy profiles and investigate the feasibility of a given substrate in VirX1-facilitated halogenation.

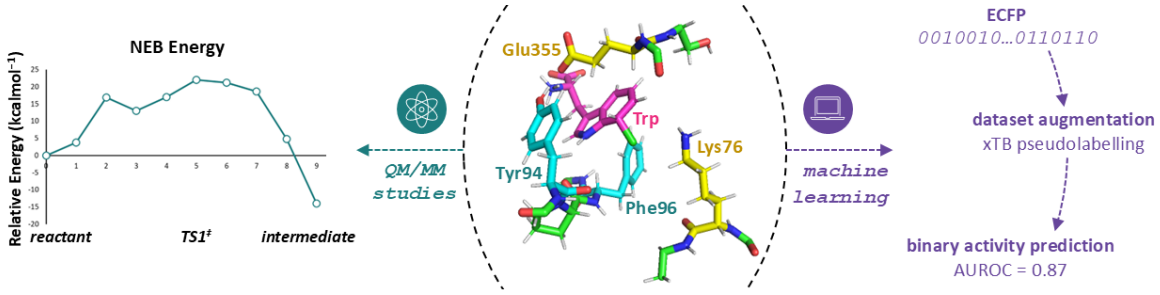

Figure 1. Summary of methods used for computational studies of VirX1 substrate scope.

To broaden the investigation, we use logistic regression to create a binary activity classifier. The model leverages an experimentally-obtained substrate-VirX1 activity dataset, with substrates represented by extended-connectivity fingerprints (ECFP), and has an area under receiver operating characteristic curve (AUROC) score of 0.80. To improve the model, we augmented the dataset with additional substrates and pseudo-labelled them with xTB-derived features such as HOMO-LUMO gap, significantly boosting the model's predictive power to an AUROC of 0.87 (p = 0.014).

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Exploration of Computational Protocols for the Study of Cu-Catalysed Reactions

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Halodeboronation reactions involving arylboronic acids are an efficient way for synthesizing aryl halides, specifically for use in medical applications such as PET (positron emission tomography) imaging. Recently, Cu-catalyzed iododeboronation of arylboronic acids was studied and a Chan-Lam-type mechanism for the catalytic cycle was proposed.[1] The extension of this iododeboronation reaction to the domain of fluoride chemistry has interesting applications.[2]

Computational studies offer critical information regarding reaction profiles and important intermediates. However, extrapolating the results from iododeboronation to fluorodeboronation can bring about some challenges owing to the nucleophilicity of fluoride ion. The polar protic solvents can interact with the fluoride ion via hydrogen-bonding, thereby modulating its reactivity. This generates an interesting question with regards to the chemical models employed in modelling studies – How to go beyond current standards of solvation modelling which employ continuum methods, for building more accurate chemical models?[3]

In this regard, we have used hybrid solvation using the cluster-continuum/microsolvation model at DFT level. Automated protocols implemented for placement of explicit solvent molecules and exploration of conformational space using global geometry optimization methods have been employed for identifying relevant candidates for this modelling study. The initial results demonstrate significant impact on the energy profile on employing hybrid solvation. Currently, our study employs a static approach to solvation, and we are interested to extend this study by investigating the dynamic behaviour (interactions) of the solvent molecules with the fluoride anion along the reaction pathway.

In this work, we aim to study the effects of microsolvation models by including explicit solvent molecules in the chemical model. Furthermore, protocols for choosing a computational model are being developed in this ongoing study by benchmarking the DFT functionals against high level ab-initio theory.

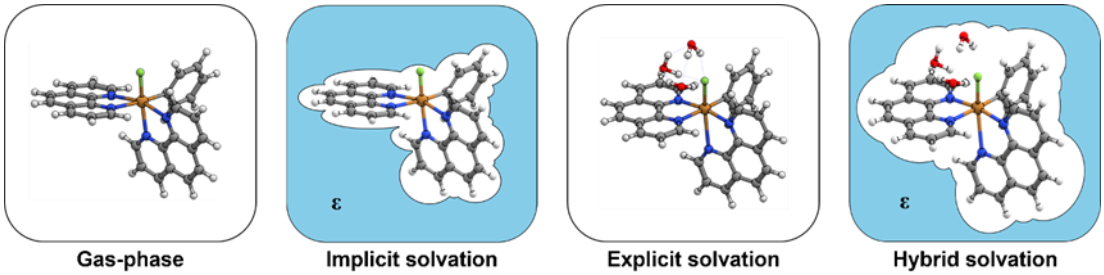

Figure 1. A representational diagram showing computational models in (a) gas-phase, (b) implicit solvent models, (c) explicit solvent models, and (d) hybrid solvent models.

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Differential Ionisation in Proton-Helium Collisions

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Ionisation is a fundamental physical process that has garnered much attention from experimentalists and theorists alike. This is because, even for few-body systems, it is not well understood. The advent of cold target recoil ion momentum spectroscopy has allowed high-precision kinematically complete measurements to take place. Theoretical descriptions of such experiments, however, have lagged behind due to the complexity of modelling a free electron travelling through the Coulombic fields of both the scattered projectile and the residual target ion. Such difficulties are compounded when considering incident energies in the intermediate range where the probability of electron capture is large, requiring the application of two-centre methods to obtain accurate results.

The two-centre wave-packet convergent close-coupling (WP-CCC) approach has been developed to address these challenges and is applied to the simplest four-body ionisation problem which is that presented by protons colliding with helium atoms. In the WP-CCC method, the scattering wave function is expanded in a set of atomic orbitals, which is then inserted into the Schrödinger equation to form a set of coupled differential equations which are solved numerically to ultimately obtain cross sections. This approach provides the opportunity to perform a comprehensive and systematic investigation of a single system, thereby bolstering confidence in the ultimate conclusions of said investigation. The most detailed quantities for studying ionisation are differential cross sections. They allow us to probe the underlying mechanisms governing the process which have remained elusive. Generally speaking, there are two broadly accepted mechanisms; direct ionisation (DI) into the continuum the target, and electron capture to the continuum (ECC) of the projectile. Other types of ionisation, such as the so-called saddle-point mechanism, have been proposed but are somewhat controversial. The merits of each proposal were investigated through the calculation of doubly [1–3] and fully differential [4,5] cross sections. The fully differential cross section is particularly instructive as it may be presented in a number of ways that illuminate different parts of the final electronic phase space. For example, multidimensional momentum distributions of ionised electrons have often been measured by experimentalists as they permit an overall picture of the ionisation process. The first ab initio calculations of these data were performed using the WP-CCC approach, leading to excellent agreement. These results along with those of less differential cross sections have not demonstrated that there is evidence to support a mechanism of ionisation that is independent of DI or ECC. This study has provided a complete and accurate account of the ionisation taking place in intermediate-energy p+He collisions.

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Conformational Isomerism Tunes Refrigeration Potential in Metal Organic Frameworks

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As the effects of climate change become more apparent in the form of rising global temperatures, the necessity for temperature control become more significant.[1] Current refrigerants are low cost and work extremely efficiently but these materials possess very high global warming potentials.[2] A greener alternative is a solid-state approach via barocaloric materials which exhibit large adiabatic temperature and isothermal entropy changes upon compression and decompression cycles.[3]

Metal-organic frameworks (MOFs) are porous, crystalline materials that are highly modular due to the many metal and linker combinations possible.[4] Notably, certain MOFs exhibit the *breathing* effect wherein the adsorption and desorption of guest molecules are accompanied by a large reversible volume change. From this, they have been recognised as potential barocaloric materials.[5]

My research combines several computational methods to explore and further understand the structure-property relationships in MOFs. We identified the existence of orientational disorder in the linkers which result in conformational isomers in the MIL-53-fum framework series. Using *ab initio* molecular dynamics (AIMD), the effects of the isomerism on the framework properties was uncovered. Grand canonical Monte Carlo (GCMC) simulations allowed us to isolate, for the first time, the entropic contributions of guest adsorption from the volumetric or conformational aspects. This revealed the role of breathing and rigid MOFs in refrigeration applications. Collectively, the results from using both techniques inform the design of functional materials, and how the barocaloric potential can be tuned with conformational isomerism. Finally, machine learning interatomic potentials (MLIPs) were trained and deployed in order to overcome the time/length scale problem. This enables a combined workflow of MC-MD to capture the full range of dynamics of the MOF during operation as a refrigerant.

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Computational Chemistry x Data Science

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Computational studies of homogeneous catalysis play an increasingly important role in furthering (and changing) our understanding of catalytic cycles and can help to guide the discovery and evaluation of new catalysts.[1-3] While a truly "rational design" process remains out of reach, detailed mechanistic information from both experiment and computation can be combined successfully with suitable parameters characterising catalysts[4,5] and substrates to predict outcomes and guide screening.[6]

The computational inputs to this process rely on large databases of parameters characterising ligand and complex properties in a range of different environments.[4,5] Such maps of catalyst space can be combined with experimental or calculated response data,[7] as well as large-scale data analysis,[8] and we are increasingly applying data science techniques for visualisation and prediction. Rather than pursuing a purely computational solution of *in silico* catalyst design and evaluation, an iterative process of mechanistic study, data analysis, prediction and experimentation can accommodate complicated mechanistic manifolds and lead to useful predictions for the discovery and design of suitable catalysts.[1-3]

In this presentation, I will use examples drawn from our recent work, including the extension of one of our ligand property databases (LKB-bid)[9] to focus on ligand effects on complexes of first row transition metals, including the structural and energetic effects of different spin states.

Website: https://feygroupchem.wordpress.com/

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