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Application of Raman Spectroscopy from MOFs to Drug Discovery

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Raman spectroscopy has been a very important spectroscopic tool, but with the advent of nano-technology, it has gained enormous potential. Unfortunately, many researchers have not used the potential of Raman spectroscopy except using it as a characterization tool. Due to the ease of doing Raman spectroscopy and its ability to give not only vibrational properties of molecules and solids but also its inter connection with electronic states and spin states gives it an edge over many other spectroscopic tools available. One can use Raman to investigate the microscopic origin of the properties of the molecules and solids. In this respect this talk aims to emphasis the use of Raman spectroscopy to investigate the microscopic origin of gas adsorption in Metal Organic Frameworks (MOFs) and understanding the small molecule therapeutic protein interaction in combination with Molecular Dynamics (MD) simulations to assist in Drug Discovery.

An unusual CO_2 adsorption behavior is seen in fluoro-functionalized MOF $\{[Zn(SiF_6)(pyz)_2]\_2MeOH\}_n$ (1) with a 1D channel system, which is made up of pyrazine and SiF_6^{2-} moieties. Surprisingly, desolvated 1 (1') adsorbs higher amounts of CO_2 at 298 K than at 195 K, which is in contrast to the usual trend. This unusual observation was revealed using Raman spectroscopic and theoretical studies. Raman spectroscopy shows that upon desolvating the pyrazine rings are slanted in 1' and reaches an angle of 17.28^0 with respect to the (200) Zn(II)–Si plane at low temperature. This block the channel windows at low temperature leading to reduce the uptake amount [1].

In another example, we have used zeolitic imidazolate framework ZIF-8, where even though the channel is equal to the kinetic diameter of CO_2 it adsorbs larger molecules such as N_2 and CH_4, but not CO_2. Raman spectroscopy was used to investigate molecular level changes in the ZIF-8 (a prototypical zeolite-like porous metal organic framework) as a function of temperature. Temperature dependent Raman spectra suggest that at low temperature the softening of the C−H stretching frequencies is due to the decrease in steric hindrance between the methyl groups of methyl imidazole. The larger separation between the methyl groups lining the channel opens the window for increased nitrogen and methane uptake at temperatures below 153 K. Since CO_2 solidifies at 195 K, it is hindered from entering the channel due to blocking done by the methyl group. The appearance of Raman bands at 2323 cm^{-1} and 2904 cm^{-1} at or below 153 K in ZIF-8 are characteristic signatures of the adsorbed nitrogen and methane gases respectively. Nanoscale ZIF-8 uptakes more molecules than bulk ZIF-8, and as a result we could provide evidence for encaged CO_2 at 203 K yielding its Raman mode at 1379 cm^{-1} [2].

In the recent years, surface enhanced Raman spectroscopy (SERS) has become an important tool to detect trace amount of analytes and has seen many technologies being developed. Since therapeutically important proteins in biologically important conditions are usually found to be in nano-Molar concentration, we have used SERS to study several proteins with an intent to understand the drug protein interaction for potential drug screening or drug discovery. As an example, we have taken the case of a selective inhibition of oncogenic Aurora A Kinase by Felodipine. This is important as Aurora A Kinase is over expressed in

most of the Tumours, but it has a very similar structure to Aurora B Kinase with only 4 amino acid residues different in the catalytic site for ATP binding. It is very difficult to get any drug to selectively bind to Aurora A Kinase due to this fact. We have used SERS and MD simulations to show that Felodipine takes advantage of a extra hystidine amino acid in the hinge region of the Aurora A Kinase of human enzyme to selectively bind to it on the surface of the Aurora A Kinase leading to reduction of access to the catalytic region for ATP binding, leading to the inhibition. Mutagenesis experiments suggest Tyr-212 is the important amino acid helping in the binding of Felodipine. We have demonstrated this through bind studies of Reversine which binds at the catalytic cite of both Aruora A/Aurora B kinase [3]

[References]

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[3] D. Karthigeyan *et al. Proceedings of National Academy of Sciences* **111**, 10416 (2014).