

Single Molecule Mechanistic Studies on Polymerase Activity

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The hepatitis C virus (HCV) is recognized as major human pathogen. Approximately 250000 infected individuals live in Canada. HCV infection is associated with severe liver disease, including cirrhosis and hepatocellular carcinoma (HCC). Unfortunately, the availability of potent inhibitors that block replication of HCV is limited, and by far not everyone benefits from therapy with pegylated interferon-alpha and ribavirin. These drugs are not HCV-specific. Severe toxic side effects, the ability of the virus to evade the host interferon system, and the enormous genetic variability of the virus are recognized as factors associated with treatment failure. A better understanding of specific steps involved in HCV RNA genome replication will likely improve the basis for the development of novel antiviral drugs with improved potency and specificity.

Here we describe experiments that are designed to: 1) gain a molecular level understanding of de novo initiation of RNA synthesis catalyzed by HCV and 2) elucidate the functional roles of the GTP binding sites in HCV. We have used Single Molecule and ensemble fluorescence resonance energy transfer, as well as fluorescence polarization studies to address the interactions between HCV and substrate oligonucleotides. We will describe these preliminary results in the presentation.

Photochemical Synthesis and Characterization of an Electrophilic Germylene by Laser Flash Photolysis of 3,4-dimethyl-1,1-bis-pentafluorophenylgermacyclopent-3-ene

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The chemistry of 3,4-dimethyl-1,1-bis-pentafluorophenylgermacyclopent-3-ene (**1**) has been characterized by laser flash and steady state photolysis. Trapping products indicate that the corresponding germylene (**2**) is indeed extruded to give the expected O-H insertion product (**3**). While direct detection of (**2**) in hexane solution remains elusive, laser flash photolysis results in coordinative solvents have shown behaviour consistent with that of a very electrophilic germylene. Specifically, coordination complexes have been detected in THF and MeOH solution characteristically blue-shifted from typical diarylgermylene complexes. Interestingly, transient spectroscopy in neat MeOH solution have shown indications of deprotonation of the complex in neat MeOH solution, consistent with that of a very electrophilic germylene – MeOH complex.

