

Machine learning approach to predict photo-induced radical generation in triphenylamine *bis*-ureas

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Triphenylamines (TPA) and their radical cations have great potential in many fields such as organic semiconductors, magnetic materials, and redox organic catalysis. The Shimizu group has reported persistent radical generation in self-assembled triphenylamine *bis*-urea macrocycles, urea-tethered TPA dimers, and urea-tethered TPA monomers on photo-irradiation. These systems show varying maximum photoinduced radical percentages which have been measured using electron paramagnetic resonance (EPR) spectroscopy. While synthetic strategies behind these molecules are reported, properties behind the photoinduced radical generation are not well established. Here in, we report a machine-learning approach that accurately predicts experimental properties related to photoinduced radical generation. A total of 18 crystal structures were used as the dataset and the maximum photoinduced radical percentage was set as the target property. The dataset consists of triphenylamine *bis*-urea macrocycles with halogen atoms at the exterior (Br), and guest molecules encapsulated inside the cavity, urea-tethered TPA dimers with exterior H, Cl, Br, I, and urea-tethered TPA monomers. To train the ML model to the experimental data, electronic- structure-based features were generated using both the density functional theory (DFT) and time- dependent (TD) DFT. Thus far, we have used four calculated features: the adiabatic ionization potential energy (eV), Transition Dipole Moment (D), Linear electron (e)/hole (h) distance (Å), and excitation energy (eV). These features were combined with several different kernel-based regression models, which achieved a cross-validation mean absolute error of 0.23% radicals. Current efforts are underway to apply this model to compounds from the Cambridge Crystallographic Data Centre (CCDC) for selection before experimental testing. This machine learning approach will provide a structure-property relationship between TPA crystal systems and photo-induced radical generation which will impart a better understanding of the experimental properties of TPA-based systems that generate photo-radicals.

Self-Assembly of Phenylethynylene *bis*-urea macrocycles in solution

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Phenylethynylene bis-urea macrocycle **1** and related fully conjugated arylene ethynylene macrocycles are shape-persistent and spontaneously assemble into ordered structures. They have applications in host-guest chemistry, chemical sensors, and organic electronics, owing to their larger length and minimum ring strain in their planar conformations. Bis-urea **1** can assemble into needle-shaped columnar crystalline materials using the bifurcated urea hydrogen bonding motif; however, the mechanism of assembly in solution remains unknown due to their poor solubility in common organic solvents. This limitation can be overcome by the introduction of a solubilizing group (1,2,3-tris(dodecyloxy)-5-ethynylbenzene) on the exterior of the macrocycle. Herein, we synthesize a soluble 1,2,3-tris(dodecyloxy)-5-ethynylbenzene phenylethynylene bis-urea macrocycle **2** and examine their assembly in solution. Dynamic covalent chemistry is employed as a synthetic strategy using diisocyanates and hindered diamines to obtain the product in good yield. The resultant macrocycle shows improved solubility in chloroform, tetrahydrofuran and 1,1,2,2-tetrachloroethane (TCE). Our goals are to probe the self-assembly mechanism in solution and evaluate strategies to stabilize individual nanotubes. Concentration-dependent NMR spectroscopy in chloroform was used to characterize the self-assembly of **2**. In NMR, a notable downfield shift of the urea protons from 4.98 ppm to 5.76 ppm is observed in chloroform at 298 K as concentration is increased from 0.1 mM to 3 mM. This shift can be attributed to intermolecular hydrogen bonding interactions suggesting the formation of supramolecular polymers. The plot of chemical shift as a function of concentration best fit to an isodesmic model. Currently, the structure and homogeneity of these assemblies are being probed by DLS, AFM, and X-ray scattering for comparison with the related crystalline assemblies. This study will aid in understanding the self-assembly mechanism of phenylethynylene bis-urea macrocycles and contribute to the design of functional materials with desired properties.

Exploring Cocrystals and Deep Eutectic Solvents based on halogen bonding for future advancements in drug development

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Halogen bonding is a noncovalent intermolecular interaction that occurs between an electrophile and a nucleophile analogous to hydrogen bonding. This is often observed in compounds containing heavy halogens like iodine and bromine. When the halogen atom is covalently bonded to another atom or molecule, preferably to an electron-withdrawing moiety, an electrophilic region (sigma hole) is created on the halogen atom on the extension of the covalent bond while a nucleophilic region is created orthogonal to the covalent bond¹. Type 2 halogen bonding in which the angle between the electrophile and nucleophile of neighboring molecules is 180° or almost linear, imparts directionality and tunability through the halogen bonding interactions. This can make extended networks such as chains, sheets, and 3D frameworks through self-assembly leading to many potential applications where structural design is important, such as in supramolecular chemistry¹, crystal engineering², and the pharmaceutical industry. The halogen bond donors are more hydrophobic compared to analogous hydrogen bond donors. Hence nearly all halogen bonded adducts are more lipophilic than analogous hydrogen bonded adducts. This feature of halogen bonding is used to enhance the drug permeability through cell membranes³. In our studies, we use iodide and triiodide alkylammonium salts as halogen bond acceptors and iodofluorobenzenes as halogen bond donors to produce cocrystals via slow evaporation of the solvent at room temperature and pressure. The crystal structures are obtained using single-crystal diffraction and are useful to develop broader structural tendencies that can be applied to materials or pharmaceutical design.

If the combination of halogen bond donors and acceptors does not produce a cocrystal, the potential implications are equally exciting. A liquid or eutectic reaction product can be characterized by thermal analysis techniques such as differential scanning calorimetry and thermal gravimetric analysis. Full mole fraction studies plotted with predicted melting temperatures reveal any deep eutectic compositions in these halogen-bonded systems. Deep eutectic solvents (DES) are considered tunable solvents and a greener alternative to ionic liquids and conventional solvents due to their low vapor pressure and more benign constituents. DESs based on hydrogen bonding are well explored in literature while those based on halogen bonding are scarce. The very first DES based on halogen bonding was reported by Peloquin and coworkers in a mixture of 0.35-0.70mol% 1,3- dithiane and 0.65-0.30mol% 1,2-diiodo-3,4,5,6-tetrafluorobenzene with the eutectic point at 13.7°C⁴. DESs are involved in applications in metal deposition and synthesis, and an emerging area of DES study is in biotransformations which convert absorbed drugs into active agents or convert toxins into less harmful substances in the body. Traditionally biotransformation is performed in aqueous solvents since polar organic solvents denature enzymes. Hence, replacing polar solvents with DESs could allow the substrate to dissolve without denaturing the enzymes⁵. In the current study, a new class of DESs produced by triiodide alkylammonium salts and iodofluorobenzenes is introduced and characterized.