

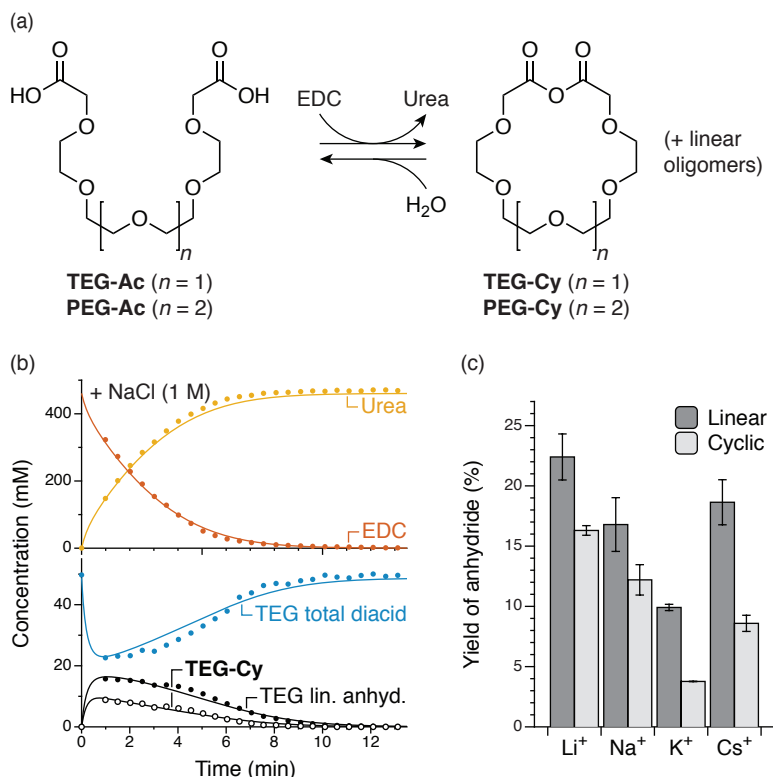
Chemically fueled dissipative (energy-expending) assembly is one of the hallmarks of biochemical systems, yet its development as a tool for abiotic systems chemistry is in its infancy. The goal of this project is to develop *carbodiimides* as useful chemical fuels for the assembly of carboxylic anhydrides, in water, from the corresponding carboxylic acids. Since anhydrides are hydrolytically unstable, they should spontaneously decompose back to the starting acids. This basic functionality, the transient formation of an unstable covalent bond, is one of the fundamental building blocks for functional systems such as molecular motors and nonequilibrium assemblies.

As outlined in the original proposal, the project has three Specific Aims: (1) The development of anhydrides as dissipative covalent bonds. (2) The construction of macrocycles using this chemistry. (3) The generation of out-of-equilibrium molecular geometry changes using this chemistry. Over the course of the second year of this grant we have completed Specific Aim 1 and much of Specific Aims 2 and 3.

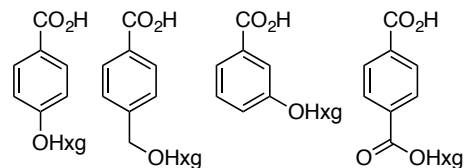
Prior to this year, we had established conditions for the transient assembly of simple commercially available carboxylic acids using the water-soluble carbodiimide EDC, a common reagent. Substantial characterization by NMR and IR spectroscopies was done to show that anhydride is indeed formed in these systems. We showed that the kinetics were readily monitored by NMR spectroscopy, and that the concentrations of all species could be fit to a simple kinetic models.

We then worked to show that this chemistry could be used to assemble more complex architectures. Initially, we explored the formation of crown-ether-like macrocycles from simple diacids, as shown in Figure 1a. In these systems, both cyclic (**TEG-Cy**) and acyclic anhydrides can be distinguished by NMR spectroscopy (Figure 1b). Interestingly, the yields of the macrocycles were found to be sensitive to the presence of alkali metal cations, as shown in Figure 1c, with the “matched” cation acting to *decrease* the yield of the macrocycle. This effect, a sort of “negative templation” by the species’ own guest, is a counterintuitive example of out-of-equilibrium effects on assembly.

Our first goal for the past year was to step back characterize the basic chemistry underlying this process. While both of the key reactions (anhydride formation and hydrolysis) are long-known reactions that have been thoroughly studied, it is important to investigate the two processes acting together in order to understand how these reactions can be used in more-complex systems. Accordingly, the assembly of the benzoic acid derivatives in Chart 1 were studied. The results are well fit by simple kinetic models, with substituent effects varying the lifetimes of the anhydrides from minutes to hours. These results should have significant implications for the design of new nonequilibrium systems making use



**Figure 1.** (a) Macrocyclization of diacids **TEG-Ac** and **PEG-Ac** fueled by EDC. (b) Typical kinetic run for the **TEG-Ac** system, in the presence of NaCl. (c) Yields of the macrocycle **TEG-Cy** and linear anhydrides in the presence of various cations.



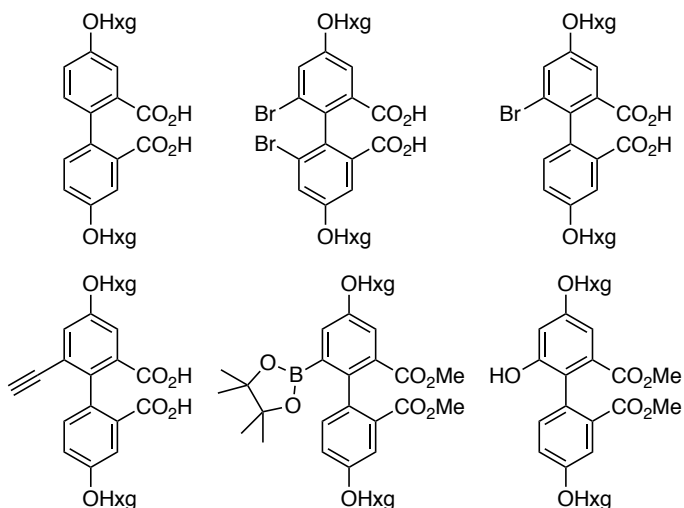
**Chart 1.** Benzoic acid derivatives used as substrates for dissipative anhydride formation.

of this chemistry. A manuscript describing these results is currently being prepared.

At the same time, we have been working on the syntheses of 6-substituted and 6,6'-disubstituted diphenic acids, which will be used to study the ability of anhydride formation to generate strain. After some effort, we have prepared a number of symmetrically and unsymmetrically functionalized diphenic acids, shown in Chart 2, which will be both useful substrates in their own right and precursors to others. Preliminary results on unsubstituted diphenic acid are promising, and we are currently beginning our first sets of kinetic measurements on these systems.

**Impact.** Prior to receiving this award, the Hartley group had specialized in characterizing phenomena at equilibrium, especially molecular folding and dynamic covalent self-assembly. These projects had typically made heavy use of organic synthesis, NMR spectroscopy, computational chemistry, UV-vis and fluorescence spectroscopies, and related techniques.

In contrast, this project, with its focus on non-equilibrium systems, is almost entirely based on observing and modeling chemical kinetics. This is a very different skill set and one with which we had essentially no experience. It was therefore especially important that the students have the time to learn new techniques, which was enabled by the research assistantships funded by the grant. It gave us the opportunity to explore new experiments, attend relevant conferences, publish our first results, and, most importantly, gather key preliminary results that have been used to obtain continuing funding for the project from the Department of Energy.



**Chart 2.** Diphenic acids (and derivatives) synthesized to date.