

## Acylphosphates as versatile transient species in reaction networks and optical catalyst screenings

Andreas Englert, Felix Majer, Jannik L. Schiessl, Alexander J.C. Kuehne, & Max von Delius\*



*Chem*, **2024**, 10(3), 910-923.

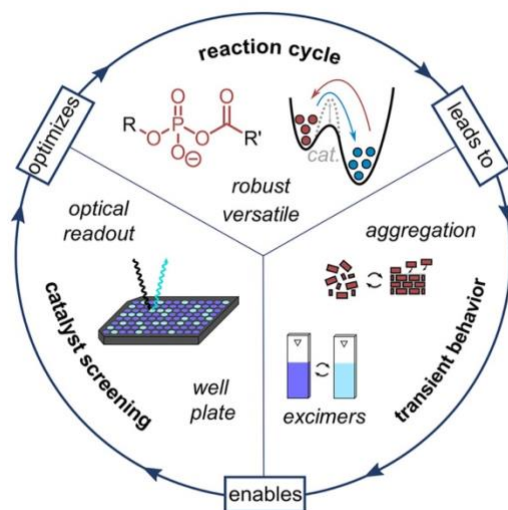


Figure 1. Big picture from the paper summarizing the main aspect of the work: i) the accumulation of high energy products, ii) transient aggregation and excimer formation iii) High-throughput optical catalyst screening.

**Prof. Dr. Max von Delius:** 2005-2006 Research internship **Prof. Jean-Marie Lehn**, 2007 Diploma studies at FAU in the group of Prof. **Andreas Hirsch**, 2010 PhD **David A. Leigh:** Synthetic Molecular Walkers, 2011-12 Postdoc **Vy M. Dong** (University of Toronto, Canada).

The author has a collection of publications focused on diverse topics including: **molecular machines**, **dynamic cryptands**, rotaxanes, synthetic carbon allotropes, etc. More in general the author interest is focused in physical organic chemistry, with a particular interest in **dynamic covalent chemistry**, **complex dynamic networks**, and organic materials.

### What is the main claim of the article?

**Artificial reaction cycles lack in robustness and versatility**, in contrast, **organophosphates** chemistry offers the possibility to build **robust** new **reaction cycles** of alkylation/hydrolysis using EDC in H<sub>2</sub>O and a nucleophilic catalyst.

The system presents **valuable performance characteristics**, outlined alongside the envisaged **application in aqueous environments**. The study is further corroborated with an optical **high-throughput screening** of different catalysts.

The work is aligned with the scope of the **Chem** journal (IF 23.5 in 2022), which focus on **fundamental studies in chemistry** with a view towards addressing **global challenges**.

## How is it demonstrated?

### 1) Network and robustness

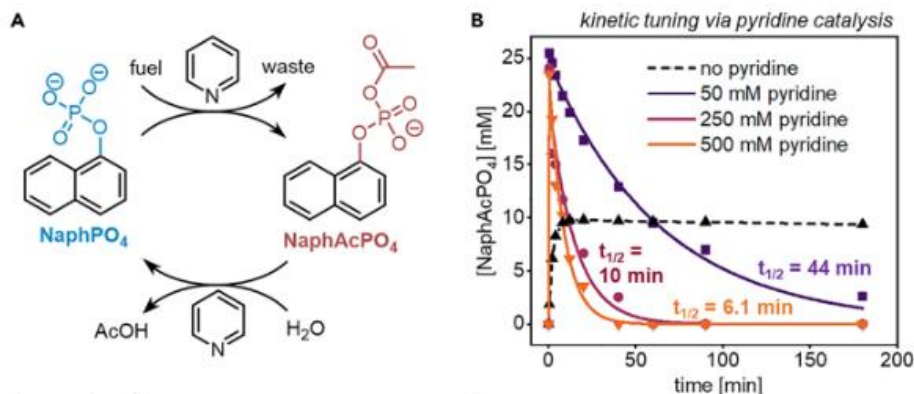


Figure 2. Reaction cycle and pyridine dependent acyl phosphate half-life.

The **acylation** of organophosphate is obtained with **two strategies**: employing **Ac<sub>2</sub>O** or **EDC/AcOH** (fuels). Both the **acylation** and the **hydrolysis** can be **catalyzed** by nucleophilic catalysis (**pyridine**). By fuel addition it is possible to access to non-equilibrium steady state with high concentration of acylated product, the subsequent hydrolysis rate depends from the amount of pyridine added.

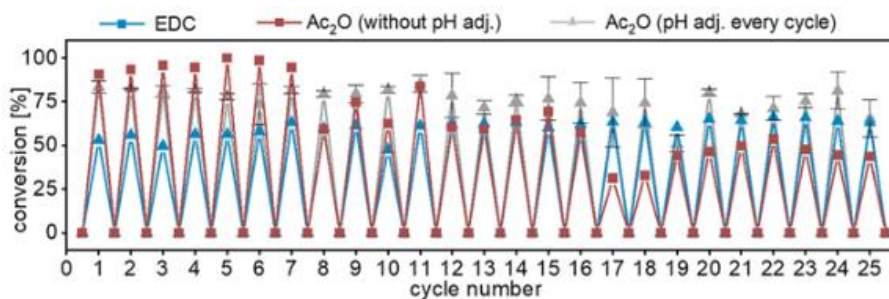


Figure 3. Fatigue test reporting 25 consecutive reaction cycles.

The reaction can be sustained for up to **25 cycles** with **no observed fatigue** for the EDC/AcOH system. When **Ac<sub>2</sub>O** is used as the fuel, 2 equivalents of AcOH accumulate per cycle, and **adjusting the pH** (by adding NaOH) is beneficial.

### 2) Catalyst screening

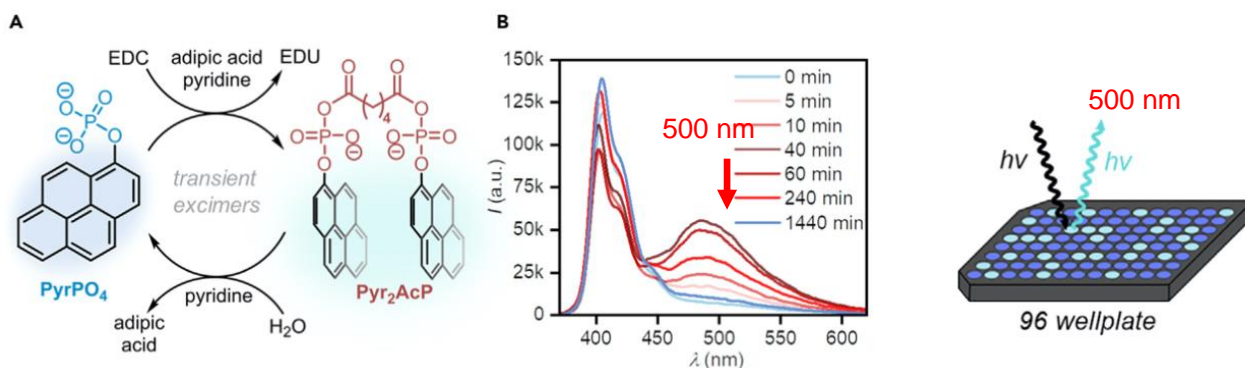


Figure 4. Pyrene dimer and excimer emission, 96 plate catalyst screening.

The reaction of adipic acid and pyrene-1-phosphate forms a **difunctionalized pyrene product** (Pyr<sub>2</sub>AcP), indicated by red-shifted **excimer** fluorescence (500 nm) due to pyrene unit interaction. The authors utilized this phenomenon for **optical catalyst screening** with a 96-well plate reader. Results: N-alkylated imidazoles and pyridines with electron-donating substituents in meta- or para-position catalyze the hydrolysis reaction most efficiently. (*maybe an obvious result*)

### 3) Scope study

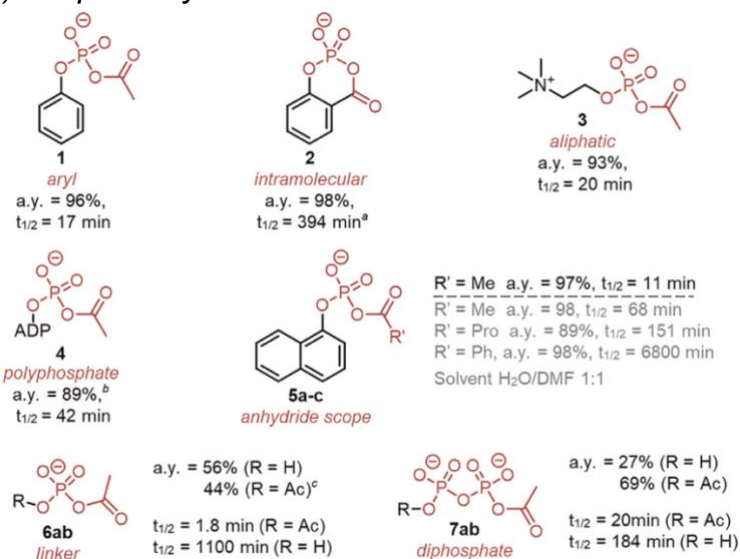


Figure 5. Scope of the work.

Activation **yield** (a.y., determined after 2 minutes of fuel addition) almost **quantitative** most of the cases indicating a great **versatility**.

The **hydrolysis** is faster (lower  $t_{1/2}$ ) for aromatic compounds **1-5a** compared to **3** and polyphosphates **4, 6a, 7a**.

The hydrolysis of the 2-fold acylated compound (**6b, 7b**) is faster because it restores the negative charge.

**Longer half-life** are observed for sterically **hindered** substates (**2, 5b, 5c**) that **disfavor nucleophilic attack**.

### What are the typical experimental conditions?

mM concentration of organophosphate, excess of pyridine, MOPS (1 and 2.5 M), or acetate buffer (1 M), T = 25°C; *EDC/AcOH as fuel*: 3 equiv of EDC, pH = 5.5. *Ac<sub>2</sub>O as fuel*: 3 equiv of Ac<sub>2</sub>O as fuel 6 equiv of NaOH, pH = 7.5.

Catalyst screening: 20 mM PyrPO<sub>4</sub>, 15 mM adipic acid, 100 mM EDC, 1 M MOPS buffer, T = 25°C, pH = 6.5, H<sub>2</sub>O : DMF (1:1). (50 catalyst evaluated: Lewis acid, phosphines, pyridines and imidazole derivatives, etc...)

### Which are the key related papers?

[1] *Eur. J. Org. Chem.*, **2016**, 2016(22), 3662-3670.

*Microreview* on **dynamic supramolecular systems** with **esters**, acetals, and orthoesters (see author's later studies on cryptands).

[2] *Chem. Eur. J.*, **2022**, 28(13), e202104116.

Publication investigating ribose derivative **dimerization to pyrophosphates**, utilizing **EDC** and **1-ethylimidazole** as nucleophilic catalysts.

[3] *ChemRxiv*, **2023**, DOI: 10.26434/chemrxiv-2023-fdkf2.

Work related from other authors (J. Boekhoven), **acyl phosphate-based protocells**

### **Additional comments, including additional elements of interest**

Thought 1: more focus about **thermodynamic**, **kinetic** parameters and quantification of **energy stored** would be needed in these systems to **compare** a particular network with other ones.

**Acylphosphates** hold an important role in pyruvate metabolism and **glycolysis**<sup>1</sup> and were recently identified as potential key molecules in the **prebiotic** world.<sup>2</sup>

Thought 2: **Phosphorous** biogeochemical **cycle** is one of the slowest one,<sup>3</sup> it is interesting wondering why Nature has chosen this element for information (DNA, RNA) and energy exchanges in living organisms...

### Ref

[1] a) *J. Chem. Educ.* 63, 566. b) *J. Bacteriol.* 175, 2793–2798.

[2] *Angew. Chem. Int. Ed. Engl.* 55, 104–121.

[3] <https://swroc.cfans.umn.edu/research/soil-water/phosphorus-cycle>

