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Efficient Catalysis of a Diels–Alder Reaction by Metallo-Vesicles in Aqueous Solution

Theo Rispens and Jan B. F. N. Engberts*

Physical Organic Chemistry Unit, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

j.b.f.n.engberts@chem.rug.nl

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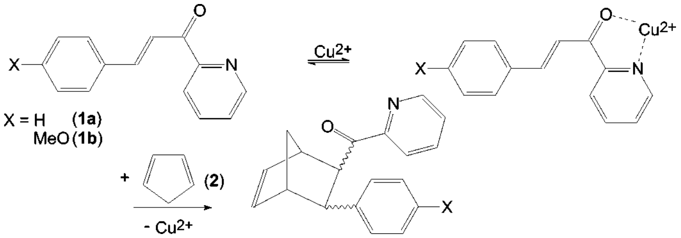
ABSTRACT



Vesicles have been prepared from a cyclic phosphate ester (5,5-di-*n*-dodecyl-2-hydroxy-1,3,2-dioxaphosphorinan-2-one) with copper(II) counterions ($Cu(dDP)_2$). They form a highly efficient aqueous Lewis acid catalyst system. The reaction of two azachalcon derivatives (1a, 1b) with cyclopentadiene (2) was studied to elucidate the catalytic potential of this system.

The use of micellar and vesicle-forming surfactants as catalysts is widespread and has been investigated in detail for many different types of reactions in aqueous solution.[1,2] Among these, surfactants with counterions acting as active catalysts form a special class.[3−9] Metallo-micelles have been reported as catalysts for several types of reactions.[3−5,8,9] Other examples include catalysis of DNA hydrolysis by cerium phosphate bilayers[10] and catalysis of aldol reactions by lanthanide dodecyl sulfate dispersions.[6,11] Herein, we report efficient catalysis of a Diels−Alder reaction by vesicles, composed of a phosphate surfactant, with copper(II) as the active counterion.

Several groups have reported bilayer structures with copper(II) as counterions[12,13] including vesicular morphology;[12] also combinations of copper ions with chelating compounds, forming bilayer[14] or vesicle[15−17] structures, are known.

We have examined the possibilities of catalyzing the Diels−Alder reactions of 3-phenyl-1-(2-pyridyl)-2-propen-1-one (**1a**) and 3-(4-methoxyphenyl)-1-(2-pyridyl)-2-propen-1-one (**1b**) with cyclopentadiene (**2**) using a combination of Lewis acid catalysis and vesicular catalysis. Previously, this reaction has been studied in different solvents, with particular

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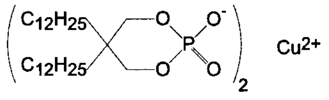
emphasis on water, both uncatalyzed and catalyzed by transition metal ions, as well as in micellar media of Me-(DS)$_2$ (Me = Ni^{2+}, Cu^{2+}; DS = di-*n*-dodecylsulfate).[9,18] The rate is significantly enhanced by using water as a solvent, as well as by using specific Lewis acid catalysts, and the combination leads to spectacular rate enhancements, even further increased by using metallo-micelles as Lewis acids.[9]

In the present study, vesicles have been prepared from equimolar amounts of the sodium salt of 5,5-di-*n*-dodecyl-2-hydroxy-1,3,2-dioxaphosphorinan-2-one (NadDP) and CuCl$_2$.[19] The size of the copper vesicles was determined using dynamic light scattering to be mainly 40 nm, with very few larger ones of about 200 nm, in accordance with EM pictures (Figure 1). The vesicles of the corresponding sodium salt are 32 nm on average, but upon addition of Cu^{2+}, fusion will most likely take place, analogous to addition of other bivalant cations.[20]



Cu(dDP)$_2$

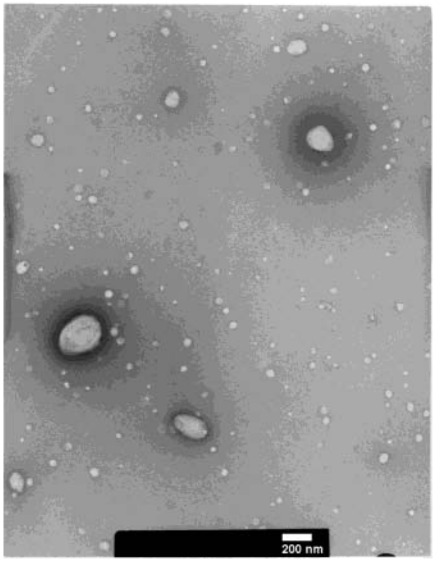


Figure 1. Electron micrograph of vesicles formed from NadDP and CuCl$_2$. The bar represents 200 nm.

Rate profiles for the reactions of **1** with **2**[22] in solutions containing Cu(dDP)$_2$ vesicles are shown in Figure 2. For comparison, the effect of Cu(DS)$_2$ micelles on the rate is shown as well. There are two observations to be made. First, the maximum rate is 1.5−2 times higher for the Cu(DS)$_2$ micelles than for the Cu(dDP)$_2$ vesicles, under the reaction conditions used. Nevertheless, the efficiency of the metallo-vesicular catalysis is extremely high, involving a rate increase relative to the uncatalyzed reaction in acetonitrile of a factor of 1 × 10^6.

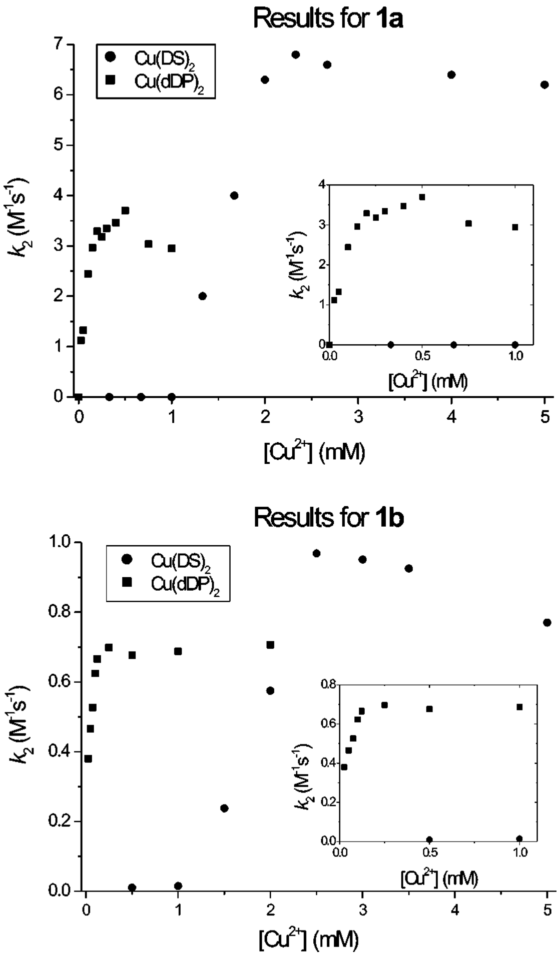


Figure 2. Rate profiles for the reaction of **1a** and **1b** in Cu(DS)$_2$ and in Cu(dDP)$_2$ solutions. The concentration of **2** is 1−2 mM. The rate constants presented are the observed (pseudo)-first-order rate constants divided by the concentration of **2**.

Not unexpectedly, the second-order rate constant did depend on the concentration of **2** in the case of Cu(dDP)$_2$ vesicles. At lower concentrations of **2** (in the range of 0.2−

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[18] Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702.

[19] Solutions were prepared by sonicating a dispersion of Na(dDP) at about 50 °C using a Branson 250 sonicator. To the resulting vesicular solutions[20] was added a concentrated stock solution of CuCl$_2$. This resulted in vesicles with an average size of predominantly 40 nm, which were stable for several days. The increase in turbidity may be caused by the appearance of a few larger vesicles. Attempts to prepare vesicles directly from the copper salt[21] failed. From the more obvious choice of surfactant, di-*n*-dodecyl phosphate, no vesicles could be prepared, as the copper salt precipitated immediately.

[20] Buwalda, R. T. Wagenaar, A.; Engberts, J. B. F. N. *Liebigs Ann. Recueil* **1997**, 1745.

[21] This salt was made by adding a saturated solution of copper(II) acetate to a concentrated solution of the acid at 50 °C,in HAc/H$_2$O 1:1, from which the copper salt precipitated.

[22] Reactions were performed at 25 °C. Concentrations were in the order of 0.2−2 mM for **2** and 0.01 mM for **1**.

0.5 mM), k_2 tends to be higher, particulary at lower concentrations of surfactant. Since the concentration of **2** is rather high compared to that of Cu(dDP)$_2$, it is likely that the size and morphology of the vesicles will be influenced by incorporation of **2**.

Most important, however, is the fact that catalysis is already observed at much lower concentrations (by a factor of 10−20) for the metallo-vesicles, as compared to the metallo-micelles (see Figure 2). This is caused by the much lower critical vesicle concentration (cvc) of Cu(dDP)$_2$, as compared to the cmc of Cu(DS)$_2$. As a result, hydrophobic microdomains are present at lower concentrations, to which both the diene and the dienophile can bind efficiently (vide infra). Cyclopentadiene will bind predominantly into the hydrophobic core of the vesicle bilayer (for Cu(DS)$_2$ micelles, similar binding characteristics were confirmed by NMR experiments[9]), whereas the dipolar dienophile will be bound at the surface of the bilayer, complexed to copper ions. In fact, the rate in the vesicular phase may even be lower than that in the micellar phase, because of the larger hydrophobicity of the inner core of the vesicles will result in a more extensive shielding of **2** from the dienophile.

An attempt was made to determine the binding strengths of the dienophiles to copper ions at the vesicular surface. Assuming that the copper ions in bulk water will not bind significant amounts of dienophile at the concentrations considered, the complexation constant of **1b** to Cu^{2+} counterions is estimated to be larger than 8500 M^{-1}.[23] This is a factor of 7 higher than the complexation constant to Cu^{2+} in water (1240 M^{-1}). The combination of binding of the dienophile to a vesicle and to a Cu^{2+} ion thus leads to an overall strongly enhanced dienophile−copper(II) binding, which accounts for the high catalytic efficiency of the copper vesicles.

At concentrations of **2** below ca. 0.5 mM, the exact method of preparation of the vesicular solutions was also of influence on the rate. Two ways of preparing solutions at a specific concentration of Cu(dDP)$_2$ were examined: (1) dilution of a "concentrated" (2 mM) stock solution and (2) direct preparation of the solution. The second method resulted in rates up to a factor of 2 higher than in the case of method 1. If, however, the solutions, prepared by method 2, were used after standing for 1−2 days, the results were similar to those from method 1. It may be that the initial size of the vesicles is smaller than the 40 nm found (vide supra) but that at higher concentrations of surfactant a rapid relaxation to slightly larger vesicles takes place. Solutions prepared by method 2 may therefore initially contain smaller vesicles. Indeed, at low (0.3 mM) concentration of surfactant, a slow increase in turbidity was observed over a period of a day using UV/vis spectroscopy. If these assumptions hold, one might speculate about why smaller vesicles would be more efficient catalysts. In this context, we note that for the alkaline hydrolysis and thiolysis of *p*-nitrophenyl octanoate it has been observed that smaller vesicles (11−30 nm vs 140 nm) are the better catalysts.[24] In this case, the main contribution to the enhanced rate has been ascribed to the more efficient binding of the substrate to the smaller vesicles. This may also be the case for the present system. Alternatively, one could imagine that in the smaller, more curved vesicles the hydrophobic diene is better accessible to the (Cu(II)-complexed) dienophile.

To summarize, vesicles formed from Cu(dDP)$_2$ are able to catalyze the Diels−Alder reaction of **1** with **2** efficiently at low (0.1 mM) concentrations, making vesicular catalysis more attractive than micellar catalysis from the viewpoint of "green chemistry". The rate depends on the exact reaction conditions, as well as on the exact method of preparing the vesicular solutions.

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[23] Because of the high affinity of the dienophile for the vesicles, it was not possible to determine *K* at concentrations of dienophile low enough to ensure no changes in vesicle morphology. Instead, we found a systematic dependence of *K* on the concentration of the dienophile.

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