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Supramolecular Chemistry

Azaphosphatrane Organocatalysts in Confined Space: Cage Effect in CO_2 Conversion

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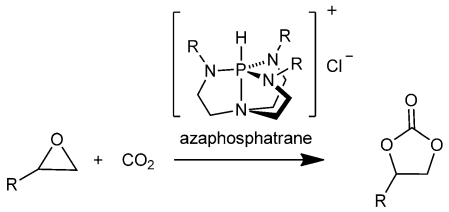
Abstract: The endohedral functionalization of a molecular cage by an azaphosphatrane unit has allowed for the creation of highly engineered catalytic cavities for efficient conversion of CO_2 into cyclic carbonates. Strong structure/activity/stability correlations have been demonstrated by careful adjustment of the size, shape, and electronic properties of the hemicryptophane host.



Scheme 1. Synthesis of cyclic carbonates from epoxides and carbon dioxide, catalyzed by azaphosphatranes.

The use of carbon dioxide (CO_2), a primary greenhouse gas, as a non-toxic and largely available C1 building block is attracting growing interest for the development of sustainable and green chemistry.[1] In particular, the conversion of CO_2 into cyclic carbonates in the presence of an epoxide is very attractive both because of the high atom economy of the reaction and for the many applications of cyclic carbonate compounds as building blocks or additives.[2] Hence, numerous catalysts have been developed for this purpose.[3] Many catalytic systems were found to be very active but, in most cases, they required fairly drastic reaction conditions and often a co-catalyst to achieve high conversions. Some systems also have the environmental drawback of the use of toxic metals. Therefore, the design of novel metal-free catalysts with enhanced properties still remains to be developed as a step towards effective CO_2 conversion. In this context, azaphosphatranes (AZAP), the acidic counterparts of proazaphosphatrane superbases,[4] proved to be original and tunable catalysts for the synthesis of cyclic carbonates from CO_2 and epoxides (Scheme 1).[5]

In particular, we have shown that the substitution pattern on the catalyst greatly affects its activity and stability. Detailed kinetic studies allowed us to propose a mechanism involving unique dual activation of both the epoxide, through hydrogen bonding, and CO_2, through insertion into the P–N bond (Figure S1 in the Supporting Information), at a single azaphosphatrane molecule. The resulting highly reactive tricyclic phosphoryl–carbamate intermediate could also be involved in the degradation process of the catalyst through the opening of the azaphosphatrane structure. We thus anticipated that the encapsulation of the azaphosphatrane catalyst in a molecular cage should avoid this deactivation pathway. Indeed, the encapsulation of an active species in a molecular cavity, as it is often observed for enzymes, can both: 1) change its reactivity inducing higher rate constants and/or new selectivities, and 2) improve its stability by protecting the catalyst from degradation.[6] Among the different structural types of supramolecular catalysts,[7] the hemicryptophane host appears very promising as it can combine a recognition site and a catalytic site.[8]

Herein, we investigate how the construction of different molecular cavities around the P–H site can change the catalytic activity and the robustness of azaphosphatranes. Caged azaphosphatranes **1a**–**d** were synthesized following a known strategy,[9,10] and tested in the cycloaddition of CO_2 with epoxides (Figure 1). For comparison, non-caged azaphosphatrane models **2a**–**d** were also prepared. As we shall see, the structural changes of the molecular cavity around the P–H site greatly influence the catalytic behavior of the encapsulated azaphosphatranes.

To study the effect of confinement on the catalytic activity of azaphosphatranes, we first compared azaphosphatrane–hemicryptophane **1a** with its open-faced analogue, **2a**, which lacks a cavity (Figure 1). The coupling of styrene oxide with CO_2 was chosen as a benchmark. Typically, the reaction was carried out over 24 h under mild conditions (1 bar, 100 °C) with a catalyst loading of 1 mol%. Both the model and encaged catalysts gave satisfactory results, with the yields of product being 73% and 82%, respectively. Thus, the catalytic properties of azaphosphatranes in the conversion of CO_2 to cyclic carbonates were not altered by encapsulation, suggesting that

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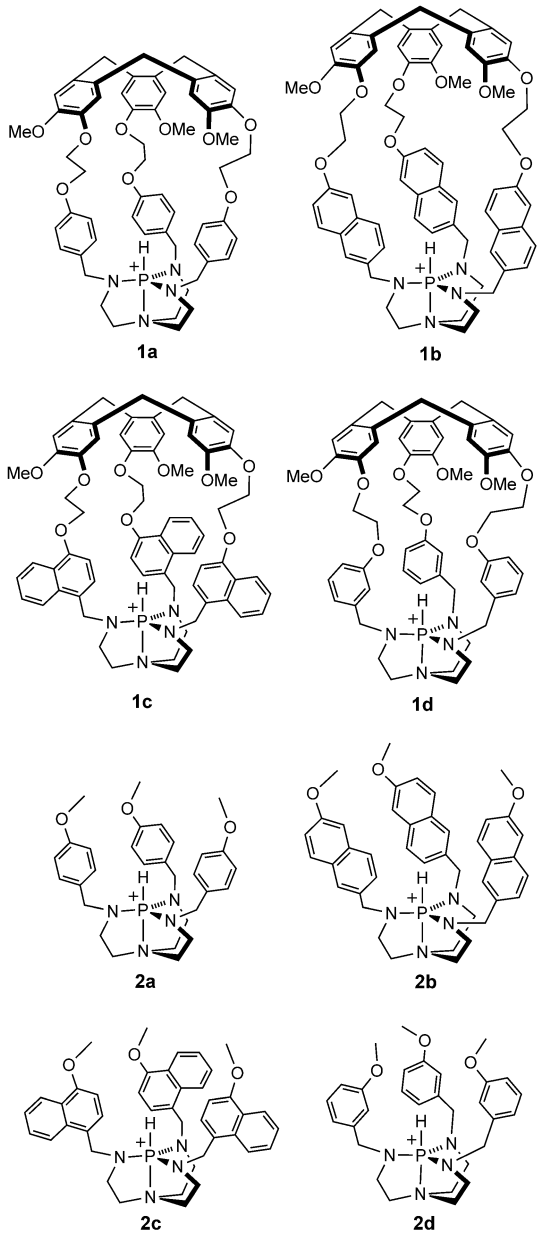

Figure 1. Supramolecular azaphosphatranes **1a**–**d** having cavities of different size and shape, and the corresponding model compounds, **2a**–**d** (counter ion: Cl^-).

supramolecular catalyst **1a** did not suffer from product inhibition. A second series of experiments was then performed with a 1000:1 epoxide-to-catalyst ratio to explore the catalyst stability over a longer period (96 h). The progress of the reaction was monitored by ^{1}H NMR analysis of aliquots taken every 24 h. After each 24 h period, an appropriate amount of styrene oxide was added to bring the substrate-to-catalyst ratio back to 1000:1.

Two main differences between the supramolecular catalyst **1a** and its model **2a** were found (Figure 2). Firstly, regarding the turnover number (TON) after 24 h, encaged azaphosphatrane **1a** was found to be twice as active as its model counterpart, thus highlighting an enhancement of the reactivity

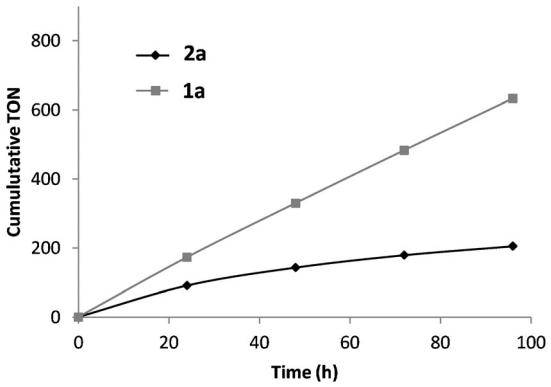

Figure 2. Effect of confinement on catalytic performances of supramolecular azaphosphatrane **1a** and its model, **2a**. Reaction conditions: styrene oxide (50.0 mmol), catalyst (0.05 mmol), CO_2 (1 bar), 100 °C. TONs were determined by ^{1}H NMR spectroscopy by using 2,4-dibromomesitylene (2.0 mmol) as an internal standard.

through encapsulation. Secondly, a steady decline in activity was observed for model catalyst **2a** over the four-day test, whereas encaged organocatalyst **1a** exhibited higher stability under these conditions, with no noticeable alteration of activity over the four-day experiment. Consequently, at the end of the reaction (96 h), the TON for the azaphosphatrane included in a hemicryptophane host was about three times higher than that of the corresponding uncapped model compound. The constraint induced by the cage structure around the phosphorus atom seems to correlate with the catalyst stability, hence suggesting that the active site is protected from degradation. These results also support our mechanism involving dual activation of epoxide and CO_2 by a single azaphosphatrane catalyst molecule. Indeed, a strong decrease of activity is expected if the activation of epoxide and CO_2 would occur at two different molecules of catalyst because both reactants would be encaged and activated in two different molecular cavities, thus greatly limiting their ability to react together.

Deeper insight into the role played by the cage structure was obtained by tuning the size and shape of the cavity above the P–H site. We first examined the catalytic activity of supramolecular catalyst **1b**, which bears bulky naphtyl linkers, and compared it to its model compound, **2b** (Figure 1). Surprisingly, under our initial reaction conditions (1 mol% of catalyst, 24 h, 100 °C, 1 bar), model catalyst **2b** was far more active than its encaged counterpart, **1b** (77% and 3% yields, respectively). Thus, the confinement imposed by the hemicryptophane structure strongly affects the performance of the AZAP organocatalyst. To more accurately probe the change of reactivity induced by the cage structure, a series of kinetic studies was carried out over a longer reaction period (4 days) at a lower catalyst loading (0.1 mol%; Figure 3a). Model catalyst **2b** was found to display behavior that was similar to that of model catalyst **2a**: good initial activity was observed, but after 24 h, the TON dramatically decreased. On the other hand, encapsulated organocatalyst **1b** showed nearly constant activity over the four days of the experiment, although its initial activity was ten times lower than that of parent model **2b**. Whereas

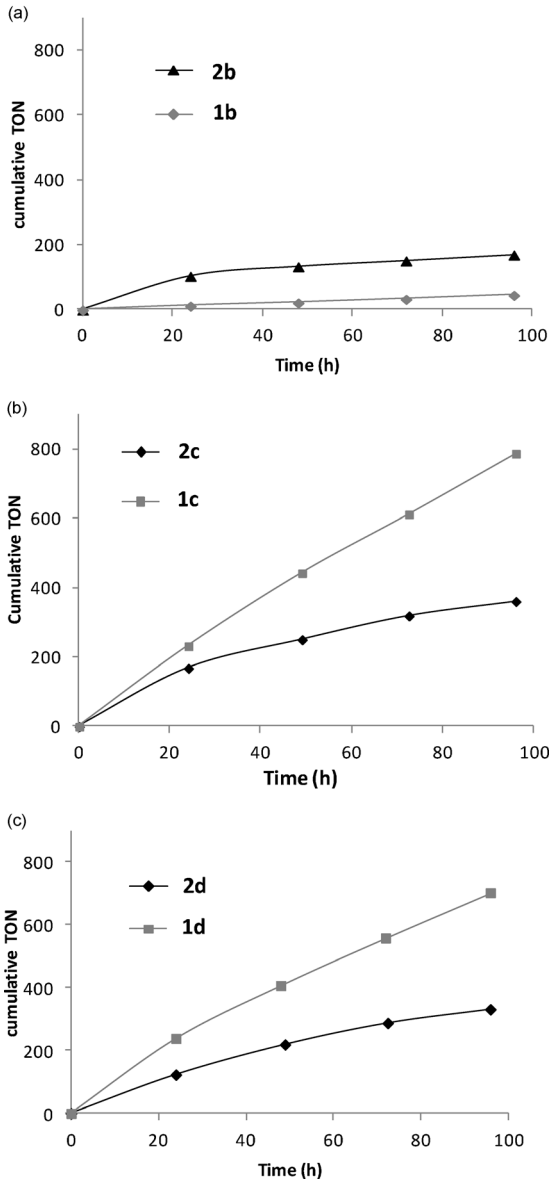

Figure 3. Influence of the architecture of the cavity on the catalytic reactivity of supramolecular azaphosphatranes **1b**–**d** and model analogues **2b**–**d**. Reaction conditions: styrene oxide (50.0 mmol), catalyst (0.05 mmol), CO_2 (1 bar), 100 °C. TONs were determined by ^1H NMR spectroscopy by using 2,4-dibromomesitylene (2.0 mmol) as an internal standard.

the two model compounds, **2a** and **2b**, displayed similar catalytic activities during the first 24 h with TONs of around 100, strong differences were observed between the related caged derivatives, the TONs for supramolecular azaphosphatrane **1a** being 15 times higher than those for **1b**.

We have recently shown that the size and shape of the molecular cavity in **1a**–**d** was strongly dependent on the nature of the linker, and examination of the X-ray structural data, when going from **1a** to **1b**, showed that the molecular cavity grew along the pseudo C_3 axis of the molecule but also became narrower (see Figure S2 in the Supporting Information).[10] Thus, access to the phosphorus site in **1b** is more restricted than in host **1a**. Recall that the proposed mechanism begins with the activation of the epoxide by hydrogen bonding to the P–H site, an interaction that should be strongly disfavored in **1b** where the helical arrangement of the naphtyl groups limits the accessibility to the phosphorus center (see Figure S3 in the Supporting Information). These results highlight the size and shape dependence of reactivity for organocatalysts based on hemicryptophane cages in the conversion of CO_2 to cyclic carbonates. These results also clearly demonstrate the crucial role of the P–H center in the AZAP structure because limiting its access by the sterically congested naphthalene linkers, strongly decreased reactivity.

To further establish the key influence of the catalytic space above the P–H center on catalytic performance, we investigated the catalytic behavior of two additional caged azaphosphatranes (**1c** and **1d**, Figure 1): **1c** provides further insight into the role played by the naphtalene unit on reactivity whereas **1d** provides information regarding a more open structure, which should lead to higher activity. Indeed, both supramolecular catalysts, **1c** and **1d**, exhibited high activity after 24 h of reaction with 89% and 84% yields, respectively, values that are close to those of their parent models (yield: 83% for **2c** and 75% for **2d**). The kinetic profiles of encapsulated catalysts **1c** and **1d** and model organocatalysts **2c** and **2d** (Figure 3b,c) mirror the behavior described above for **1a** and **2a**. Encaged azaphosphatranes **1c** and **1d** displayed constant catalytic activities over the four-day experiments, whereas those of model parent catalysts **2c** and **2d** dramatically decreased over the same period.

These results are in agreement with our hypothesis. Firstly, they confirm that the change of reactivity induced by the naphthalene unit is related to change of the available space around the reactive center and not to specific electronic properties of the naphthalene moiety. Furthermore, these trends highlight how the inner-cavity volume and the accessibility to the P–H site affect the reactivity of the encaged azaphosphatrane (the TONs for **1c** after 24 h were found to be 1.5 and 23 times higher than those for **1a** and **1b**, respectively). Thus, protection of the reactive site by encapsulation allowed TONs of greater than 700 to be achieved, thus making **1c** and **1d** remarkably active and stable supramolecular organocatalysts. The preorganization of the molecular cage likely reinforces the ability of the catalytic core to maintain its atrane structure during the catalytic cycle, thus improving its stability. Indeed, the loss of catalytic activity observed for all the model compounds may originate from the instability of the phosphoryl–carbamate intermediate formed after CO_2 insertion into the P–N bond.[11] The constraint induced by the cage structure around the phosphorus atom should favor the regeneration of the polycyclic structure of the azaphosphatrane unit at the end of the catalytic cycle (see Figure S1 in the Supporting Information). This behavior underlines the relevance of hemicryptophane hosts for designing efficient and modular supramolecular catalysts.[8c] Indeed, most of the known supramolecular catalysts suffer from product inhibition and have to be used in stoichiometric amounts. On the contrary, hemicryptophane compounds are rather flexible, as previously observed,[9] allowing for greater lability of the host–guest association, in

particular, an easy release of the carbonate product, behavior that may account for the remarkable efficiency for catalytic CO_2 conversion observed here.

In summary, specific tailor-made nanoreactors based on the hemicryptophane host, each defining a specific confined space around a catalytically active azaphosphatrane, have been designed and successfully applied to the synthesis of cyclic carbonates from CO_2 and epoxides. Varying the shape of the space above the reactive center has allowed a unique study, which demonstrated how the nature of the nanospace of the molecular cavity can dramatically affect the stability and reactivity of the organocatalyst: the caging of the active site not only increases the catalytic activity, but also prevents its degradation by protecting it from deactivation pathways. This study also brought to light new evidence concerning the previously proposed mechanism involving the simultaneous dual activation of the epoxide and CO_2 at a single azaphosphatrane molecule.

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Keywords: azaphosphatranes · CO_2 conversion · cyclic carbonates · green chemistry · organocatalysis

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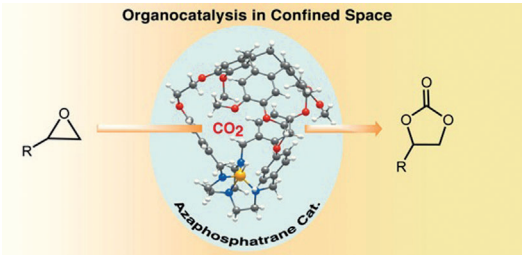

Combining supramolecular chemistry with CO_2 conversion into cyclic carbonates has led to efficient and robust encaged organocatalysts. The remarkable properties of azaphosphatranes toward this reaction were not only retained but magnified by encapsulation in a supramolecular hemicryptophane structure. These results also support the proposed mechanism involving dual activation of both the epoxide and CO_2 at a single azaphosphatrane molecule.

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