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COMMUNICATIONS

Published on Web 04/08/2008

Organocatalysis In a Synthetic Receptor with an Inwardly Directed Carboxylic Acid

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The intramolecular ring-opening reaction of epoxides continues to raise issues in physical organic and bioorganic chemistry. Early studies of this reaction were used to define the stereoelectronic effects governing cyclization processes.[1–4] Current efforts are revealing the effects of solvation on this reaction in solution[5–7] and in the hydrophobic interiors of enzymes.[8–11] Of specific interest are the factors directing the course of the reaction to afford either five- or six-membered ring products (Figure 1). We report here the epoxide ring-opening cyclization reaction of epoxyalcohols within the structured environment of a cavitand. The results from our study highlight the special reactivity provided by cage structures[12–16] bearing functional groups on their concave surfaces.[17–20]

Cavitand **1** is a deep, open-ended receptor built up from a resorcinarene scaffold[18,21,22] and functionalized with a Kemp's triacid derivative (Figure 2).[23] The cavitand can fold around suitable guest molecules, isolate them from the bulk solution, and present them with an inwardly directed carboxylic acid. This vase-like conformation is stabilized by a seam of hydrogen bonds conferred by a cyclic array of secondary amides around the rim of the receptor. These amides make up a polar region in the receptor and, together with the inwardly directed acid, can participate in host−guest hydrogen bonding interactions. Likewise, the receptor's eight aromatic walls may be regarded as immobilized benzenes that offer an electron-rich π-surface to bound substrates. Taken together, these features provide bound guests with a unique solvation and an arrangement of organic functionality that are otherwise unavailable in solution. In this study, we investigated the reaction of 1,5-epoxyalcohols **3**−**5** in the synthetic receptor **1** and in solution using model acid **2** (Figure 3).

Upon adding epoxyalcohol **3** to a solution of **1** in mesitylene-d_{12}, we observed immediate host−guest complexation as indicated by the characteristic signals in the upfield region of the ^{1}H NMR spectrum (Figure 4a).[24] The conversion of epoxide **3** into ether **6** was monitored by the disappearance of the starting material resonances at 2.43 ppm and the appearance of product resonances at 3.52 ppm (in bulk solution). The five-membered ring (THF) ether **6** *was the exclusive product of the reaction*. In contrast, the solution-phase reaction of epoxyalcohol **3** with camphorsulfonic acid afforded an 87:13 ratio of the THF to tetrahydropyran (THP) products.[25] The synthetic receptor **1** provided a >50-fold rate acceleration over the reaction using acid **2** as the comparator ($t_{1/2\text{cavitand}\mathbf{1}} = 7.2$ h, $t_{1/2\text{acid}\mathbf{2}} = 16$ days).[26]

Cavitand **1** also catalyzed the cyclization reaction of alcohol **4**. In this case, the reaction provided a 1:1 mixture of THF and THP products (**7a** and **7b**, Figure 4b).[27] Although no regioselectivity was observed in this reaction, the cavitand provided a >300-fold rate acceleration over the analogous reaction using

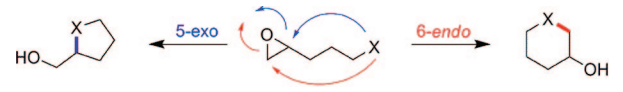

Figure 1. The 5-*exo* versus 6-*endo* modes of cyclization for epoxide ring-opening reactions.

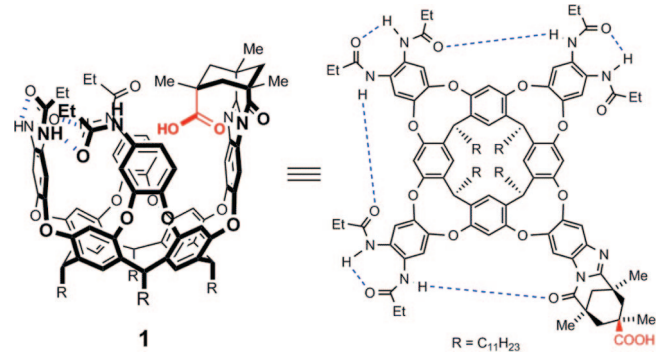

Figure 2. Cavitand **1** represented in its folded vase-like conformation (left) and as its detailed Lewis structure (right).

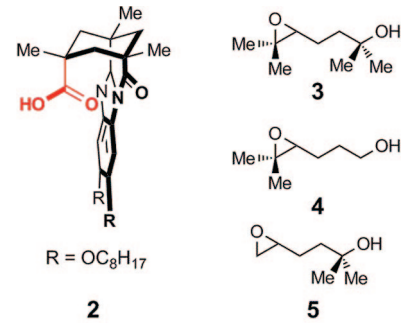

Figure 3. Model acid **2** and the 1,5-epoxyalcohols **3**−**5** used in this study.

the model acid **2** ($t_{1/2\text{cavitand}\mathbf{1}} = 8.9$ h, $t_{1/2\text{acid}\mathbf{2}} = 114$ days). The upfield chemical shifts of the guest resonances in the complexes of **4** and **1** were not as pronounced as those in the case of epoxyalcohol **3** (Figure 4a).[25] This indicated that the guest was not bound as deeply within the receptor or was not positioned as close to its aromatic walls.[28]

Regiocontrol over the cyclization reaction was restored in the case of alcohol **5**. Cavitand **1** catalyzed the formation of the THF product **8** as the exclusive product.[29] In this case, the epoxyalcohol **5** was closely associated with the aromatic walls of the receptor **1** as indicated by the large upfield shift of guest resonances in the ^{1}H NMR spectrum (Figure 3c).[28] Moreover, the 5-*exo*-tet cyclization of epoxide **5** inside cavitand **1** corresponded to >100-fold rate

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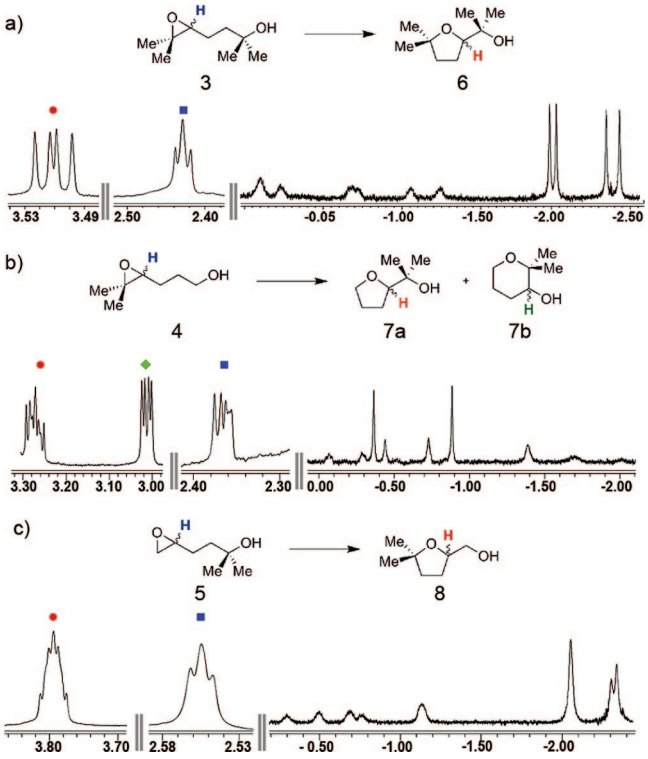

Figure 4. Sections of the ^{1}H NMR spectra of the reactions of alcohols **3** (a), **4** (b), and **5** (c) inside introverted acid cavitand **1**. Regions of the spectra corresponding to the starting epoxides are marked with blue squares. Regions of the spectra corresponding to the product ethers are marked with either red circles and/or green diamonds.

enhancement over the control reaction with using model acid **2** ($t_{1/2\text{cavitand}\mathbf{1}} = 5.3$ h, $t_{1/2\text{acid}\mathbf{2}} = 27$ days).

Several factors may be responsible for the rate enhancement observed in this system. First, molecular recognition is involved (as it is in any bimolecular reaction), but the substrate is more or less surrounded by the catalyst of finite capacity. Second, complexation exposes the epoxyalcohol substrates to a high local concentration of a Brønsted acid.[18] Third, CH-π contacts between the concave π-surface of the host and the alkyl backbone of the guest induce the coiling of the substrate inside the cavitand.[30–32] Such coiling brings the reactive centers of the epoxyalcohols in close proximity, folding the substrates into conformations resembling the transition-state structures of the cyclization reactions.

The coiling of substrates inside the cavitand can also explain the regioselectivity observed in this reaction.[30–32] The aromatic walls of cavitand **1** form multiple CH-π contacts with the geminal methyl groups at the alcohol terminus of substrates **3** and **5**. These interactions are believed to impose strong conformational control over these acyclic epoxyalcohols. Such binding limits the conformational flexibility of these guests within the cavitand and directs the reactions to proceed via the compressed five-membered-ring transition-state structures leading to THF products. Primary alcohol **4** garners fewer CH-π contacts[33] with the aromatic walls of the receptor and is consequently less conformationally constrained. For this reason, the acyclic alcohol **4** enjoys greater flexibility within the cavitand and undergoes reaction through both the compressed five-membered ring and the more extended six-membered ring transition-state structures leading to both THF and THP products **7a** and **7b**.

In conclusion, the synthetic receptor **1** binds and controls the conformation of 1,5-epoxyalcohol substrates **3**−**5**. The inwardly directed carboxylic acid functionality initiates the cyclization of these substrates to afford the five- and six-membered ring products **6**−**8**. This synthetic system incorporates the arrangement of functionality and the unique solvation provided within the structured interiors of natural enzymes. In contrast to flexible receptors for selective recognition,[34] these cavitands catalyze the regiocontrolled transformation of epoxyalcohols into cyclic ethers. A full account of the kinetic and mechanistic studies of this system will be reported in due course.

Acknowledgment. We are grateful to the Skaggs Institute for Research, and the National Institutes of Health (GM 27932) for financial support. S.R.S. thanks the San Diego Foundation Blasker Science and Technology Fellowship for financial support. S.R.S. and F.P.C. thank Prof. Dr. Yoshiki Morimoto for helpful correspondence on structural determinations, and Dr. Laura B. Pasternack for assistance with NMR spectroscopy.

Supporting Information Available: Detailed experimental procedures and kinetic study data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA801107R