Solvent-Responsive Metalloporphyrins: Binding and Catalysis

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A cholate-functionalized tetraphenylporphyrin (H_2CFTPP) was obtained by attaching eight cholate units at the meta positions of the phenyl rings. Zn(CFTPP) favored binding a hydrophilic pyridyl ligand over a hydrophobic analogue in nonpolar solvents such as 20% MeOH/CCl_4 but had the reverse selectivity in 95% MeOH/CCl_4. Tunability of the ligand binding resulted from the cholates that aggregated intramolecularly to form either unimolecular micelle-like or reversed micelle-like structures, depending on solvent polarity. The micelle-like structures appear to be less well organized than the reversed micelle-like conformations and might be induced by hydrophobic guests. The solvent-dependent intramolecular aggregation of cholates was used to tune the catalytic activity of an iron porphyrin derivative. Epoxidation catalyzed by Fe(CFTPP)Cl gave a selectivity of up to 10:1 for alkene substrates differing by only one or two hydroxyl groups.

Introduction

Conformational control is a strategy employed by nature to achieve selectivity and regulate activity in enzymes. According to the induced-fit model,[1] the substrate of an enzyme can "turn on" catalysis by bringing the catalytic groups into proper alignment, whereas a nonsubstrate, even having the same reactive group, remains untransformed because it cannot induce the necessary conformational change in the enzyme. Signal molecules—referred to as effectors and inhibitors, depending on whether the molecule activates or deactivates the catalyst—can alter the conformations of allosteric enzymes and, consequently, serve to regulate their properties.[2] Chemists have long been intrigued by these features of biological catalysts but, until now, have not been able to develop a general approach toward conformationally controllable catalysts.[3] In recent years, there has been great interest in developing synthetic oligomers (i.e., foldamers) that can adopt biomolecule-like, folded conformations.[4] Advancements in conformational control in synthetic molecules will not only shed light on how biomolecules fold and function but also enable the development of synthetic counterparts with similar responsive and tunable properties.

We have been interested in using cholic acid as a building block to construct both foldamers[5,6] and nonfoldamers[7−9] whose conformations and properties can be reversibly switched. With a large steroid backbone that positions hydrophilic and hydrophobic groups on opposing faces, cholic acid is uniquely suited for solvophobically driven conformational changes. Previously, we synthesized an amphiphilic "molecular basket" by coupling four cholates to a cone-shaped, 4-aminocalix[4]arene scaffold.[7] The molecule adopts micelle-like conformations in polar solvents with the hydrophilic (α) faces turned outward and reversed micelle-like conformations in nonpolar solvents with the α faces inward.[10] In this article, we extend the concept to construction of a solvent-responsive metalloporphyrin. Both its binding and catalytic properties can be altered using solvent polarity as the stimulant. Through this strategy, substrates that differ by only one or two hydroxyl groups remote from the reactive site (i.e., a C═C bond) can be clearly distinguished by the metalloporphyrin.

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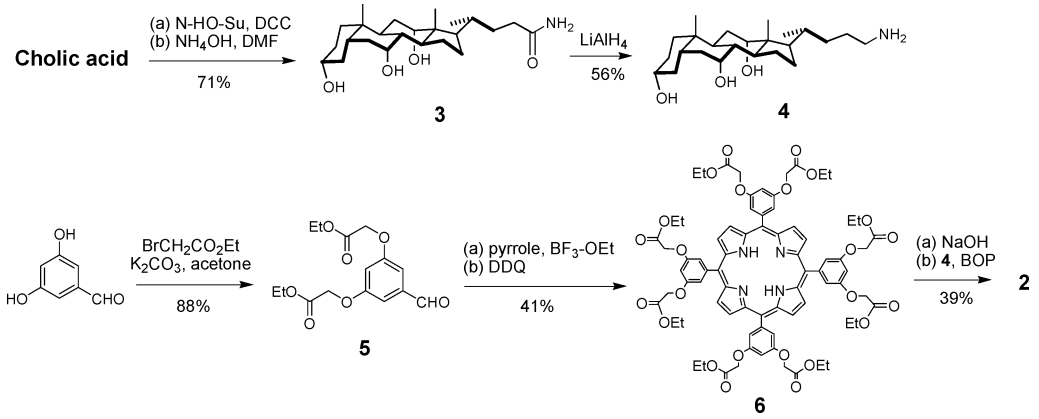
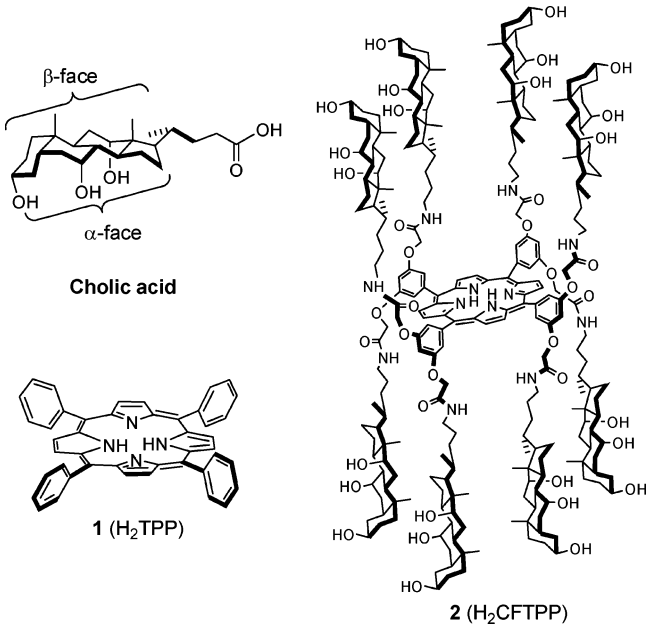
Scheme 1. Synthesis of H_2CFTPP (2)



Results and Discussion

Design and Synthesis. Metalloporphyrins were chosen as the catalytic platform for several reasons. First, they are important catalysts in both biological and synthetic transformations such as olefin epoxidation, alkane hydroxylation, cyclopropanation, and a range of other reactions.[11] Second, they can tolerate many functional groups and solvents. Common polar groups such as hydroxyls, amides, and ethers do not interfere with their catalysis. Third, the phenyl groups in tetraphenylporphyrin (**1**; H_2TPP) are nearly perpendicular to the porphyrin plane,[12] and



introduction of functional groups with predictable spatial orientation is possible on the phenyl rings. Hence, for the octacholate-functionalized tetraphenylporphyrin (**2**; H_2CFTPP),[13] it is reasonable to expect that the four cholate units can interact intramolecularly to create microenvironments above and below the catalytic site (i.e., metalloporphyrin) that can be used to regulate the activity/selectivity of the catalyst.[14]

H_2CFTPP (**2**) was synthesized using the route shown in Scheme 1. Cholic acid was converted to the *N*-hydroxysuccinimide ester using dicyclohexylcarbodiimide (DCC) as the coupling reagent. The activated ester was transformed into the cholate amide **3**, which was reduced by $LiAlH_4$ to afford the amino cholate **4**. To obtain the octaester porphyrin **6**, 3,5-dihydroxybenzaldehyde was first alkylated with ethyl 2-bromoacetate. The resulting ester-substituted benzaldehyde **5** was condensed with pyrrole in the presence of a Lewis acid, $BF_3 \cdot OEt_2$, to afford the desired product **6** in 41% yield.[15] After basic hydrolysis of **6**, the resulting octacarboxylic acid was coupled to amine **4** using benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) to afford H_2CFTPP (**2**).

Binding Properties. The scaffolds used in all the previously synthesized cholate-derived molecular baskets were "compact".[7–9] For example, the distance between the two opposite amino groups in 4-aminocalix[4]arene is about 6−8 Å according to a CPK model. In these structures, close proximity of the cholates allows efficient intramolecular association. The TPP scaffold, however, is larger—the distance between the two meta hydrogens on the phenyl rings across the porphyrin is about 15 Å. Therefore, a potential concern for H_2CFTPP (**2**) was whether the cholates could interact intramolecularly to create a microenvironment over the two faces of the porphyrin. Without intramolecular micellization or reversed micellization, the cholates would have little effect on the catalytic behavior of the metalloporphyrin. Another possible problem was that a cholate might prefer to interact with the other cholate on the same phenyl ring instead of with the other three cholates on the same side of the porphyrin face. In this case, intramolecular association of cholates occurs, but in four pairs that probably would not be able to significantly influence the catalytic activity.

In order to address these questions, we synthesized three derivatives of 4-aminomethylpyridine by acylating the amino

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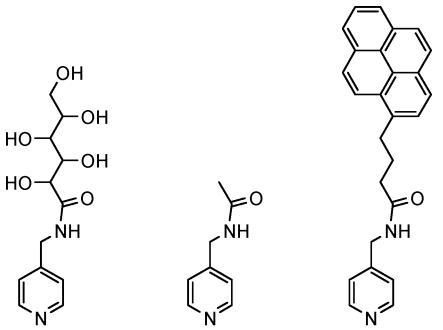
Table 1. Association Constants (K_a, in M^{-1})[a] between Zn(CFTPP) and Several Pyridine Guests at 20 °C in Different Solvents

	solvent composition						
	CCl_4/MeOH						CCl_4/DMSO
guest	5/95	20/80	40/60	60/40	80/20	90/10	90/10
7	50 ± 10	100 ± 10	100 ± 10	760 ± 340	3100 ± 1800[b]	*c*	*d*
8	5 ± 2	12 ± 1	12 ± 2	15 ± 2	50 ± 2	70 ± 2	130 ± 20
9	170 ± 50	90 ± 20 (80 ± 20)	60 ± 40	90 ± 10	90 ± 20 (120 ± 10)	210 ± 10 (230 ± 30)	<1[e]

[a] Determined by UV titrations. Numbers in parentheses were obtained from ^{1}H NMR titrations. The errors are from nonlinear least-squares curve fitting. [b] Determined by NMR dilutions. [c] The guest is not soluble in this solvent mixture. [d] Not determined. [e] Binding was too weak to be measurable.

group with a hydrophilic (**7**), a "neutral" (**8**), and a hydrophobic (**9**) group. If the proposed intramolecular micellization or



7 **8** **9**

reversed micellization does happen, the hydrophilic ligand **7** should be preferred by Zn(CFTPP) in nonpolar solvents and the hydrophobic analogue **9** in polar media (also see the idealized scheme in the table of contents entry). Compound **8** is a control used to investigate the general solvent effect for Zn−pyridine complexation. Because the different functional groups in **7**−**9** are remote and "insulated" from the pyridyl nitrogen by the saturated methylene bridge, electronic effects should be negligible in the comparison of the binding of **7**−**9**.

A pyridyl ligand normally complexes with zinc porphyrin in a 1:1 ratio.[16] We chose pyridyl ligands instead of previously used, generic hydrophilic or hydrophobic guests such as phenyl β-D-gluocopyranoside or pyrene[8] because the functionalized pyridines can probe the environment above/below the metal center. Generic hydrophilic and hydrophobic guests may be bound, but not necessarily near the metal center. Because minimal amounts of materials could be used in UV spectroscopic studies due to the intense absorption of porphyrin derivatives, the majority of data were obtained from UV titrations. All titration experiments were performed at concentrations where intermolecular aggregation was negligible.[17] The association constants (K_a) between Zn(CFTPP) and **7**−**9** are summarized in Table 1. A ^{1}H NMR dilution test was used for **7** in 20% MeOH, as the guest was not sufficiently soluble to titrate the host. In some cases (e.g., ligand **7** in 40% MeOH), solubility problems prevented coverage of a broad range of guest concentrations, and the errors from nonlinear least-squares curve fittings were larger than in other cases. In selected cases, both ^{1}H NMR and UV titrations were performed, and the results from the two methods generally showed good agreements.

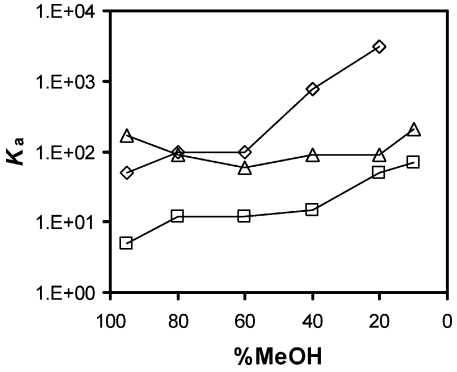


Figure 1. Plots of K_a between Zn(CFTPP) and **7** (◇), **8** (□), or **9** (△) as a function of percent MeOH in MeOH/CCl_4. The data points are connected to guide the eye.

For the control compound **8**, there is a *gradual* increase of K_a with a decrease of methanol in the solvent mixture. This result is not surprising, because alcohol is also a known ligand for zinc porphyrin.[16] Since CCl_4 is a much weaker ligand, an increase in methanol makes the solvent better able to compete with **8** for the metal center and reduce its apparent binding affinity. For the hydrophilic ligand **7**, changes in K_a are more dramatic, especially with more nonpolar solvent mixtures. For example, K_a is hardly changed in 95, 80, and 60% methanol—this is a trend similar to that observed for **8**—but increases by 30-fold over 60−20% methanol; however, over the same range of solvent polarity, the increase is less than 4-fold for **8**. For the hydrophobic ligand **9**, on the other hand, K_a displays an unusual increase toward the *polar* end of solvent composition. The association constant is 60 M^{-1} in 60% methanol but increases to 90 M^{-1} in 80% methanol and further to 170 M^{-1} in 95% methanol. Although these changes are not large, they clearly go in *opposite* trends as compared to those for **7** and **8**.

The general trends in K_a are clear in Figure 1, in which the binding constants are plotted on a logarithmic scale against the percentage of methanol in the solvents. The overall shapes of the curves for the hydrophilic ligand **7** and the control **8** are similar, except that the increase in K_a toward the low-MeOH end is more pronounced for the former. The curve for the hydrophobic ligand **9** is quite different—binding is stronger in both the high- and low-MeOH solvents but is weaker in solvents with intermediate polarity.

These binding constants generally seem to be consistent with the predicted conformational changes. As expected, the nonpolar ligand **9** is preferred by Zn(CFTPP) in methanol-rich solvents but is less preferred than the hydrophilic ligand **7** in CCl_4-rich cases. In addition, the preference in binding is more noticeable at the polar/nonpolar extremes than in the intermediate region of the polarity scale. All these observations suggest that the local environment above/below the metalloporphyrin binding site is influenced by the cholates. Collective (tetrameric) aggregation of cholates over the two faces of the porphyrin is probably more reasonable than aggregation in four pairs, as

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(17) UV titrations were performed with Zn(CFTPP) at 0.03 mM concentration. Peak broadening of resonances observed by ^{1}H NMR spectroscopy indicated that intermolecular aggregation became significant at higher concentrations (ca. 1 mM), especially in low-polarity mixtures (<20% methanol).

localized aggregation around the peripheral phenyl groups is unlikely to significantly influence ligand binding to the zinc center.

However, some comparisons are not consistent with our initial predictions. For example, we had predicted that binding of **8** would be stronger than that of **7** but weaker than that of **9** in polar, methanol-rich solvents. This is because, if indeed a micelle-like conformer is formed, it should repel **7** from its nonpolar interior. Instead, **8** is found to be a weaker ligand than **7** in methanol-rich solvents. Is the micelle-like conformer still formed in Zn(CFTPP)? If not, why is **9** bound more strongly than **7** or **8** in polar solvents? Our previous work[8,9] suggests that direct contact of the β faces is required for the normal micelle-like conformation—this is similar to the case for micelles of surfactants formed through direct contact of the hydrophobic tails. Such a direct contact, however, is less likely to occur over the large face of the porphyrin. Therefore, the most likely possibility is that the micelle-like conformer is not formed in the absence of **9** but is *induced* by its presence. Hydrophobic binding between **9** and Zn(CFTPP) reduces solvophobic exposure of both the guest and the cholate β faces of the host and, thus, may have promoted intramolecular micellization. If this is the case, stronger binding of **7** than of **8** is understandable. With multiple OH/NH groups on both the host and **7**, it is easy to imagine that some intermolecular hydrogen-bonding interactions, albeit not very strong in solvents such as 95% MeOH/CCl_4, can make **7** a better ligand.

With inwardly facing hydrophilic α faces of the cholates, the reversed-micelle-like conformer can enrich MeOH solvents within its interior from a mostly nonpolar solvent mixture such as 10% MeOH/CCl_4.[7−9] This is not surprising, because reversed micelles formed by surfactants often also need to be stabilized by a pool of water molecules in the center.[18] For this reason, we initially thought, as Zn(CFTPP) adopts the reversed-micelle-like conformation with decreasing polarity, the hydrophobic ligand **9** would be "repelled" by the entrapped polar methanol. However, its K_a increases from 90 to 210 M^{-1} when methanol is decreased from 20 to 10% (Table 1). One factor clearly contributing to this unpredicted increase is methanol being a competitive ligand for Zn—lower methanol always strengthens binding, as seen in the binding of **8** in different MeOH/CCl_4 mixtures. This factor, however, cannot explain why the increase in K_a for **9** over 20−10% methanol is even higher than that for **8**.

Although the behavior of Zn(CFTPP) supports the proposed conformational responses, the comparison between **7**/**9** and the control **8** was unexpected. Is there another important factor not considered? Since **8** and **7**/**9** also differ greatly in their size, is it possible that a larger guest is inherently preferred over a smaller one? Note that **8** (□) is a weaker ligand than **7**/**9** (◇/△) in every MeOH/CCl_4 composition (Figure 1). Polar solvents are known to be enriched from the nonpolar environment into the basket during reversed micellization.[7−9] During binding, some of these polar molecules (methanol in this case) will be displaced by the guest. Undoubtedly, larger guests such as **7** and **9** will "release" more solvent molecules than small ones (e.g., **8**). This desolvation is favorable on one hand, because the solvents are no longer constrained locally, but is unfavorable on the other hand, because the hydrogen bonds between the polar groups (NH/OH) of the cholates and methanol will be broken. It is entirely possible that such a release of solvent is overall a favorable process for methanol, especially if methanol is only loosely associated with the α faces of the cholates.

According to our previous studies, DMSO solvates the α faces of cholates more strongly than MeOH.[5−9] For example, to stabilize the reversed-micelle-like conformer in a mixture of polar/nonpolar solvents, DMSO was more effective than methanol as the polar component.[5,8] The irony is that the same preferential solvation that helps stabilize this conformer also makes it an inferior host at the same time, because DMSO is much more difficult to be displaced than methanol by the guest. This contrast between DMSO and methanol once again is found in the Zn(CFTPP) case. Whereas replacement of 10% methanol by DMSO in CCl_4 enhances the binding of the control ligand **8** by slightly less than 2-fold, it *weakens* the binding of **9** to the point of nondetection (Table 1). Apparently, once the reversed-micelle-like conformer is filled with the strongly associating polar DSMO solvent, the hydrophobic guest is indeed "repelled" and becomes a much weaker ligand than the control. Therefore, the size of the guest can be quite important, especially when significant desolvation occurs during the binding process.[19]

Overall, these binding studies indicate that the preference for different guests by Zn(CFTPP) can be tuned. Nonpolar guests are preferred in polar solvents and polar guests in nonpolar ones. The reversed micelle-like conformer seems to be better formed than the normal micelle-like one. Because the possibility of a guest-induced conformational change always exists, the actual conformation of Zn(CFTPP) is not very clear in the absence of guests. Nonetheless, it will be interesting to see if the solvent-dependent intramolecular aggregation of cholates can be used to regulate catalysis.

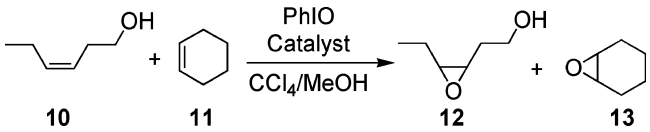
Catalytic Epoxidation. Iron(III) porphyrins were compared as catalysts for the epoxidation of alkenes. Fe(TPP)Cl was obtained commercially, and H_2CFTPP was metalated according to standard procedures to produce Fe(CFTPP)Cl. In our screenings, iodosylbenzene (PhIO), a common oxidant used in metalloporphyrin-catalyzed epoxidation, was found to be compatible with the MeOH/CCl_4 solvent system. DMSO was quickly oxidized under the reaction conditions and thus could not be used. Reactions of monosubstituted terminal alkenes such as 3-buten-1-ol were slow. As alkyl substitution and cis stereochemistry both enhance the rate of epoxidation,[11a] we chose to study the epoxidation of *cis*-3-hexen-1-ol (**10**) and cyclohexene (**11**). According to the proposed conformational changes, Fe(CFTPP)Cl should prefer a hydrophilic substrate over a hydrophobic substrate in nonpolar solvents but reverse its selectivity in polar solvents, as long as the two substrates are not too different in their inherent reactivities. Because **10** and **11** are only marginally different regarding hydrophilicity/hydrophobicity, it was not clear initially whether Fe(CFTPP)Cl could detect such a small variation.

Competition experiments were used to determine the relative reactivities of the two substrates. The benefit of competitive reactions is that the two substrates are subject to identical conditions; thus, even small changes can be reliably determined. In general, the catalyst, Fe(TPP)Cl or Fe(CFTPP)Cl, was used at 5 mol % based on PhIO. An excess (5 equiv) of each substrate is present in the solution. The reactions were allowed to continue for 3 h at room temperature under a nitrogen atmosphere, after which the yields of **12** and **13** were determined by GC analyses. Dodecane was used as the internal standard, and the yields were

(18) Fendler, J. H. *Membrane Mimetic Chemistry*; Wiley: New York, 1982; Chapter 3.

(19) It should be mentioned that this inherent preference for larger guests by Zn(CFTPP)—as well as the potential hydrogen bonding interaction discussed previously—is also consistent with **8** being a weaker ligand than **7** in polar solvents.

Table 2. Competitive Epoxidation of *cis*-3-Hexen-1-ol and Cyclohexene by Fe(CFTPP)Cl and Fe(TPP)Cl[a,b]



	Fe(CFTPP)Cl			Fe(TPP)Cl		
CCl_4/MeOH	**12** (%)	**13** (%)	**12**/**13**	**12** (%)	**13** (%)	**12**/**13**
90/10	37	7	5/1	17	9	2/1
80/20	23	6	4/1	15	15	1/1
70/30	20	8	2.5/1	10	15	0.7/1
60/40	15	11	1.4/1	15	21	0.7/1
40/60	9	10	1/1	8	17	0.5/1
20/80	8	11	0.7/1	5	15	0.3/1

[a] Reactions were carried out at room temperature for 3 h under N_2. [catalyst] = 1 mM. [catalyst]/[PhIO]/[**11**]/[**14**]/[**15**] = 0.05/1/5/5/5. [b] Yields are based on iodosylbenzene and were determined by GC analysis. The numbers given are the average yields from three separate experiments. As shown by Table 1S in the Supporting Information, the results from these separate runs are generally in excellent agreement.

based on the initial amount of PhIO added. The results are summarized in Table 2.

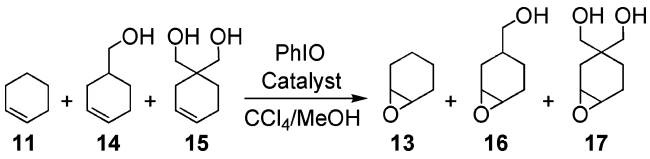
According to the data, 3-hexen-1-ol becomes more favored than cyclohexene by Fe(CFTPP)Cl with a decrease of methanol in the solvent mixture (Table 2, left). In the most nonpolar solvents, 10% MeOH in CCl_4, the preference for the "hydrophilic" 3-hexen-1-ol is 5:1 over the completely nonpolar cyclohexene. In the most polar solvents, 80% methanol in CCl_4, cyclohexene becomes slightly favored by the catalyst. Therefore, selectivity of the cholate-derived catalyst toward the two substrates indeed can be tuned by solvent composition. The 0.7:1 (=**12**:**13**) to 5:1 transition is not large, but the trend is consistent with the proposed conformational change. When control experiments with Fe(TPP)Cl were performed, however, a similar, albeit smaller, solvent effect was observed (Table 2, right). Since the ratio of **12** to **13** is always higher for Fe(CFTPP)Cl than for Fe(TPP)Cl, the data can be adequately explained by a higher activity of Fe(CFTPP)Cl toward 3-hexen-1-ol.

Nonetheless, the two substrates only differ in one hydroxyl group regarding hydrophilicity/hydrophobicity; thus, any noticeable effect caused by cholate substitution should be significant. Because the two substrates also differ in other structural features (i.e., linear vs cyclic), it is tempting to imagine that a conformationally related solvent effect is operating but may have been overwhelmed by other effects. Therefore, further studies based on more reasonable comparisons using three substrates with the same reactive cyclohexenyl substructure (Table 3) were performed.

Fe(TPP)Cl and Fe(CFTPP)Cl behave completely differently toward three cyclohexenes that vary only at positions several bonds away from the olefin. For example, whereas the product ratio **13**:**16** stays essentially the same (1:1) from the most polar (80% methanol) to the most nonpolar solvent (10% methanol) with Fe(TPP)Cl (Table 3, right), the yield of **16** is nearly 10 times as high as that of the unhydroxylated **13** in reactions catalyzed by Fe(CFTPP)Cl (Table 3, left). For the most hydrophilic product **17**, a decrease in MeOH from 80 to 10% causes almost no change in its yield (i.e., from 3 ± 1% to 4 ± 1%) with Fe(TPP)Cl but doubles the yield from 4 ± 1% to 8 ± 1% with Fe(CFTPP)Cl.[20]

(20) The yields given are the averages from three separate experiments. The errors are the standard deviations. See Table 2S in the Supporting Information for the actual yields.

Table 3. Competitive Epoxidation of Cyclohexene Derivatives by Fe(CFTPP)Cl and Fe(TPP)Cl[a,b]



	Fe(CFTPP)Cl		Fe(TPP)Cl	
CCl_4/MeOH	**13**/**16**/**17** product yield (%)	**13**/**16**/**17** product ratio	**13**/**16**/**17** product yield (%)	**13**/**16**/**17** product ratio
90/10	2/15/8	0.1/1/0.5	9/9/4	1/1/0.5
80/20	4/14/7	0.3/1/0.5	9/9/5	1/1/0.5
60/40	5/14/5	0.4/1/0.4	8/7/3	1/1/0.4
20/80	7/13/4	0.5.1.0.3	6/6/3	1/1/0.5

[a] Reactions were carried out at room temperature for 3 h under N_2. [catalyst] = 1 mM. [catalyst]/[PhIO]/[**11**]/[**14**]/[**15**] = 0.05/1/5/5/5. [b] Yields are based on iodosylbenzene and were determined by GC analysis. The numbers given are the average yields from three separate experiments. As shown by Table 2S in the Supporting Information, the results from these separate runs are generally in excellent agreement.

Moreover, the amount of product **17** increases more than that of **16** from lowering solvent polarity. For instance, when MeOH is reduced from 80 to 10%, the yield of **16** increases slightly from 13 ± 1% to 15 ± 1%, but the yield of **17** goes from 4 ± 1% to 8 ± 1%.[20] These differences are small but are in line with our prediction that the reversed micelle-like catalyst would prefer hydrophilic substrates over hydrophobic ones in nonpolar solvents. Although the yield of the most hydrophilic product **17** is still lower than that of **16** even under the most nonpolar conditions, this "discrepancy" is simply a result of the inherent higher reactivity of **14** over **15**, which is evident in the control experiments.

The different behaviors of Fe(TPP)Cl and Fe(CFTPP)Cl is even more clearly seen when the yields of the three products are plotted against solvent composition (Figure 2). With the control catalyst Fe(TPP)Cl, the yields of **13**, **16**, and **17** all display a gradual increase with a decrease in the percentage of methanol (Figure 2a). With the cholate-functionalized Fe(CFTPP)Cl, however, the more polar products **16** (□) and **17** (◇) are formed at the expense of the less polar product **13** (△) as the solvent becomes less polar (Figure 2b). The "crossover" of the most hydrophilic product (◇) and the most hydrophobic product (△) is most significant and is exactly what is expected from the proposed conformational change.[21]

Conclusions

The conformational behavior of the cholate-functionalized porphyrin complex is not as well-defined as previously synthesized amphiphilic baskets constructed on "compact" scaffolds such as calix[4]arene. With a large scaffold, solvophobic interactions are less effective at controlling intramolecular aggregation of the cholates. However, even with these more diffuse structures, conformational changes can still have a significant impact on the binding and catalysis of the metallo-

(21) Fe(CFTPP)Cl was noticeably more soluble than Zn(CFTPP), which was shown to aggregate intermolecularly at ca. 1 mM in <20% MeOH in CCl_4. Due to its paramagnetic nature, the extent of aggregation for Fe(CFTPP)Cl could not be determined by ^{1}H NMR spectroscopy. It should be mentioned that any potential intermolecular aggregation of Fe(CFTPP)Cl in low polarity solvents would only reduce the contribution of the reversed micelle-like conformer and decrease the substrate selectivity. Therefore, the observed preference for polar substrates should represent the lower limit achievable by the reversed micelle-like conformer.

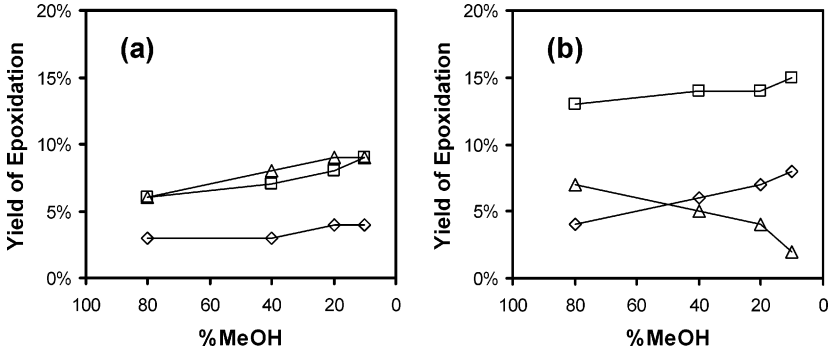


Figure 2. Percent yields of **13** (△), **16** (□), and **17** (◇) in 3 h at room temperature as a function of function of percent MeOH in CD_3OD/CCl_4 using (a) Fe(TPP)Cl and (b) Fe(CFTPP)Cl as the catalysts. The data points are connected to guide the eye.

porphyrin derivative. In a mostly polar mixture, a nonpolar ligand (**9**) is preferred by Zn(CFTPP), whereas a polar ligand (**7**) is favored in a mostly nonpolar mixture. When several alkenes (**11**, **14**, and **15**) differing only in one or two hydroxyl groups are epoxidized, selectivity toward the substrates can be tuned by solvent polarity with Fe(CFTPP)Cl as the catalyst but is unchanged when the control catalyst Fe(TPP)Cl is used. In the ideal case, the catalyst should have well-defined conformational states, each of which should have well-formed binding pockets. Such is not the case with **2** as the ligand, because the micelle-like conformation may not be formed except in the presence of large hydrophobic guests. This is probably why the hydrophobic substrate **11** was never favored over **14**, even under the most polar conditions. Much improvement is still needed, but conformational control clearly can be a very powerful tool for regulating the activity and selectivity of synthetic catalysts.

Experimental Section

General Methods. Chloroform was distilled from anhydrous K_2CO_3. Anhydrous tetrahydrofuran (THF) and methylene chloride were dried by passage through a column of activated alumina under nitrogen. Pyrrole was distilled over CaH_2 at atmospheric pressure. Stock solutions of $BF_3{\cdot}Et_2O$ were prepared by diluting $BF_3{\cdot}Et_2O$ (Aldrich, 8.1 M) to 2.5 M in $CHCl_3$ and were used within 2 weeks. Cholic acid was crystallized from 95% ethanol and dried at 90 °C under vacuum. All other reagents and solvents were of ACS certified grade or higher and were used as received from commercial suppliers. Compounds **3** and **4** were synthesized from adapted literature procedures.[22] Details of these syntheses can be found in the Supporting Information. Fe(TPP)Cl was used as received.

All glassware and syringes were dried in an oven at least overnight prior to use. Routine ^1H and ^{13}C NMR spectra were recorded on Varian VXR-300 and VXR-400 spectrometers. MALDI-TOF mass spectra were recorded on a Thermobioanalysis Dynamo mass spectrometer. UV−vis spectra were recorded at ambient temperature on an HP 8452 spectrometer. Capillary gas chromatography was performed on an HP-5890 instrument equipped with a flame ionization detector. Peak areas were measured by electronic integration using an HP 3395 A integrator.

Compound 5. To a solution of 3,5-dihydroxybenzaldehyde (438 mg, 3.17 mmol) in acetone (10 mL) was added anhydrous K_2CO_3 (2.28 g, 16.5 mmol), ethyl bromoacetate (0.92 mL, 8.3 mmol), and a catalytic amount of NaI. The mixture was stirred at room temperature overnight. It was diluted with water (20 mL) after acetone was removed in vacuo. The mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified with column chromatography over silica gel using hexane/ethyl acetate (2/1) as the eluent to give **5** as a white solid (869 mg, 88% yield). ^1H NMR (300 MHz, $CDCl_3$; δ): 9.88 (s, 1H), 7.03 (d, 2H, J = 2.4 Hz), 6.78 (t, 1H, J = 2.4 Hz), 4.66 (s, 4H), 4.28 (q, 4H, J = 7.2 Hz), 1.31 (t, 6H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$; δ): 14.3, 61.8, 65.7, 108.7, 108.8, 138.7, 159.7, 168.4, 191.5. Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.15; H, 5.94. Found: C, 58.06; H, 5.85. EIMS (m/z): M^+ 310.

Compound 6. An oven-dried, three-necked, 3 L, round-bottomed flask equipped with a magnetic stirring bar and a gas-dispersion tube was charged with **5** (2.53 g, 8.18 mmol). Chloroform (820 mL) distilled over K_2CO_3 was transferred to the flask through a cannula. Pyrrole (0.57 mL, 8.18 mmol) was added via a syringe. The solution was purged with nitrogen for 20 min. Boron trifluoride diethyl etherate (2.5 M solution in CH_3Cl, 0.49 mL, 1.23 mmol, 0.15 equiv) was added via a syringe, and the flask was wrapped with aluminum foil to shield it from light. The solution was stirred under nitrogen at room temperature for 24 h. DDQ (1.39 g, 6.12 mmol) was added in one portion. The mixture was then heated to 65 °C for another 4 h. The mixture was then cooled to room temperature, and triethylamine (6.5 mL) was added. The reaction mixture was concentrated in vacuo. The residue was purified with column chromatography over silica gel using CH_2Cl_2/ethyl acetate (20/1) as the eluent to give **6** as a purple solid (1.19 g, 41% yield). ^1H NMR (300 MHz, $CDCl_3$; δ): 8.88 (s, 8H), 7.73 (d, 8H, J = 2.1 Hz), 6.97 (t, 4H, J = 7.2 Hz), 4.92 (s, 16H), 4.27 (q, 16H, J = 7.2 Hz), −2.95 (s, 2H) ppm. Anal. Calcd for $C_{76}H_{78}N_4O_{24}$: C, 63.31; H, 5.83; N, 3.89. Found: C, 63.77; H, 5.49; N, 3.91. EIMS (m/z): M^+ 1432. UV (CH_2Cl_2; λ_{max}, nm (ϵ)): 421 (543 000), 455 (17 200), 514 (20 600), 549 (6000), 588 (6300), 645 (3300).

H_2CFTPP (2). To a solution of **6** (180 mg, 0.13 mmol) in THF (40 mL) and MeOH (10 mL) was added aqueous 1 M NaOH (10 mL). The mixture was stirred at room temperature for 2 h. The bottom purple aqueous layer was separated from the top light yellow organic layer and was acidified with 1 M HCl to pH ∼2 while the solution was kept at 0 °C. The green precipitate was collected by centrifugation, washed with water (twice) and MeOH (three times), and dried in vacuo (122 mg, 81%). A portion of this acid (88 mg, 0.224 mmol), **4** (30 mg, 0.025 mmol), and ((benzotriazol-1-yl)-oxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP; 99 mg, 0.225 mmol) were dissolved in anhydrous DMF (6 mL). Diisopropylethylamine (62 mg, 0.448 mmol) was added via a syringe. The reaction mixture was stirred at 60 °C for 24 h under N_2 and was poured into brine (50 mL). The solid was collected by suction filtration, washed with water (2 × 10 mL), and purified by preparative TLC (SiO_2, 4:1 $CHCl_3$:CH_3OH) to give a reddish powder (51 mg, 48% yield). ^1H NMR (300 MHz, $CDCl_3/CD_3OD$; δ): 8.88 (s, 16H), 8.14 (s, 16H), 7.36 (s, 16H), 7.06 (s, 8H), 4.63 (s, 32H), 4.28 (d, 16H, J = 4.2 Hz), 3.95 (d, 16H, J = 1.8 Hz), 3.82 (d, 16H, J = 0.9 Hz), 3.56 (br s, 16H), 3.07 (br s, 40H), 2.10 (q, 16H, J = 9.6 Hz), 1.97 (m, 16H), 1.95−0.55 (m, 232H), 0.37 (m, 16H), 0.05 (s, 24H). ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$; δ):

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169.2, 157.4, 144.3, 119.5, 115.3, 102.3, 72.7, 71.6, 67.6, 46.6, 45.9, 41.8, 41.3, 39.6, 39.4, 39.2, 35.4, 35.3, 34.6, 34.5, 33.0, 29.9, 28.2, 27.4, 3.3, 25.9, 22.6, 22.2, 17.0, 11.6. MALDI-TOFMS (*m*/*z*): calcd for $C_{252}H_{375}N_{12}O_{40}$ $[M + H]^+$, 4212.72; found, 4206.2.[23] UV (CH_2Cl_2/CH_3OH; λ_{max}, nm (ϵ)): 422 (129 500), 514 (13 200), 548 (6700), 590 (6200), 646 (4700).

Zn(CFTPP). $Zn(OAc)_2 \cdot 2H_2O$ (6 mg, 0.024 mmol) and **2** (35 mg, 0.0083 mmol) were mixed in CH_3OH (5 mL). The mixture was stirred at room temperature for 3 h. Brine (50 mL) was added to the solution. The precipitate was collected by suction filtration and washed with water and CH_3CN to give a dark reddish powder (34 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD; δ): 8.85 (s, 32H), 8.15 (br s, 32H), 7.37 (s, 32H), 7.04 (s, 16H), 4.63 (s, 32H), 4.28 (d, 16H, $J = 4.2$ Hz), 4.01 (d, 16H, $J = 2.1$ Hz), 3.89 (d, 16H, $J = 1.8$ Hz), 3.69 (s, 16H), 3.49 (s, 16H), 3.09 (m, 40H), 2.32−0.74 (m, 232H), 0.38 (s, 24H). ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD; δ): 169.1, 156.8, 149.9, 132.7, 126.8, 117.0, 72.9, 72.9, 71.9, 71.6, 70.3, 68.0, 67.6, 57.1, 47.0, 46.4, 46.2, 41.8, 41.7, 41.6, 39.7, 39.7, 39.4, 39.2, 35.6, 35.4, 34.9, 34.9, 34.9, 34.8, 34.5, 33.1, 31.6, 31.5, 30.0, 29.8, 29.7, 28.2, 27.7, 26.6, 26.4, 26.0, 23.1, 23.0, 22.4, 22.3, 21.1, 21.0, 17.3, 12.2. MALDI-TOFMS (*m*/*z*): calcd for $C_{252}H_{372}N_{12}O_{40}Zn$ $[M + H]^+$, 4276.1; found, 4276.5. UV (CH_2Cl_2/CH_3OH; λ_{max}, nm (ϵ)): 427 (356 100), 557 (26 500), 597 (16 100), 633 (16 000).

Compound 7. Compound **7** was synthesized according to a literature procedure.[24] 4-Aminomethylpyridine (520 mg, 4.81 mmol) and δ-gluconolactone (850 mg, 4.80 mmol) were dissolved in pyridine (10 mL). The reaction mixture was heated to reflux for 12 h and was poured into CH_2Cl_2 (100 mL). The solid was collected by suction filtration and was washed with CH_2Cl_2 (2 × 20 mL) to give a white powder (1.090 g, 75% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 8.44 (dd, 2H, $J = 4.5$ Hz, $J = 1.8$ Hz), 8.33 (t, 1H, $J = 6.3$ Hz), 7.26 (dd, 2H, $J = 4.5$ Hz, $J = 1.5$ Hz), 4.59−4.50 (m, 3H), 4.40−4.22 (m, 3H), 4.09 (dd, 1H, $J = 5.1$ Hz, $J = 3.6$ Hz), 3.96 (m, 1H), 3.60−3.32 (m, 4H).

Compound 9. 4-Aminomethylpyridine (100 mg, 0.93 mmol), 1-pyrenebutyric acid (266 mg, 0.92 mmol), and BOP (452 mg, 1.11 mmol) were dissolved in anhydrous DMF (10 mL). Diisopropylethylamine (320 mg, 2.30 mmol) was added via a syringe. The reaction mixture was stirred at 50 °C for 12 h and was poured into brine (100 mL). The solid was collected by suction filtration, washed with water (2 × 20 mL), and purified with column chromatography over silica gel using $CHCl_3$/CH_3OH (4/1) as the eluent to give a white powder (218 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$; δ): 8.44 (dd, 2H, $J = 3.3$ Hz, $J = 1.2$ Hz), 8.25 (d, 1H, $J = 6.9$ Hz), 8.14 (d, 2H, $J = 6.0$ Hz), 8.06 (dd, 2H, $J = 5.7$ Hz, $J = 3.3$ Hz), 8.00 (s, 2H), 7.97 (dd, 1H, $J = 6.0$ Hz, $J = 5.4$ Hz), 7.81 (d, 1H, $J = 6.0$ Hz), 7.05 (dd, 2H, $J = 3.3$ Hz, $J = 1.2$ Hz), 5.84 (br s, 1H), 4.36 (d, 2H, $J = 4.8$ Hz), 3.39 (t, 2H, $J = 5.4$ Hz), 2.29 (m, 2H), 2.22 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ): 172.7, 149.8, 149.3, 136.9, 131.4, 130.9, 129.8, 128.7, 127.9, 127.9, 127.7, 127.0, 126.5, 125.4, 125.2, 124.8, 124.7, 123.9, 122.6, 96.0, 41.7, 35.4, 32.8, 28.0. MALDI-TOFMS (*m*/*z*): calcd for $C_{26}H_{23}N_2O$ $[M + H]^+$, 379.5; found, 380.7.

Fe(CFTPP)Cl. Insertion of iron was accomplished using a modified literature procedure.[25] A three-necked, round-bottomed flask was charged with **2** (52 mg, 12.4 μmol) and anhydrous $FeCl_2$ (63 mg, 494 μmol) in a glovebox. Anhydrous DMF (5 mL) was added via a syringe. The mixture was heated to reflux for 3 h. After the mixture was cooled to room temperature, dilute hydrochloric acid was added in small portions. The dark reddish precipitate formed was collected by centrifugation, washed with water, and dried in vacuo (50 mg, 94% yield). MALDI-TOFMS (*m*/*z*): calcd for $C_{252}H_{372}N_{12}O_{40}Fe$ $[M - Cl]^+$, 4265.5; found, 4265.1. UV (CH_2Cl_2/MeOH; λ_{max}, nm (ϵ)): 414 (88 100), 569 (9400), 608 (4500).

UV Titrations. The host was titrated with different amounts of the guest, and absorption at the Soret band of the complex was monitored. A typical procedure is as follows. Stock solutions of Zn(CFTPP) (0.10 M) and **7** (0.14 M) in CH_3OH/$CHCl_3$ (50/50) were prepared. CCl_4/MeOH (20/80, 3.0 mL) was added to a cuvette, to which an aliquot (2.0 μL) of the stock solution of **7** was added via a microsyringe. The sample was vortexed for 1 min. The UV absorbance at 433 nm was measured. The binding constant was determined by nonlinear least-squares curve fitting of the titration data.

^{1}H NMR Titrations. A ^{1}H NMR dilution experiment was performed with equimolar amounts of Zn(CFTPP) and **7**, and the chemical shifts of the pyridyl protons in the guest were monitored. For the binding of **9**, Zn(CFTPP) was titrated with different amounts of the guest. A typical procedure is as follows. Stock solutions of Zn(CFTPP) (0.010 M) and **9** (0.10 M) in CH_3OH/$CHCl_3$ (50/50) were prepared. To 14 separate vials, 12.0 μL of the Zn(CFTPP) stock solution was added, followed by 5.0, 7.0, 9.0, 11.0, 14.0, 17.0, 21.0, 25.0, 31.0, 38.0, 48.0, 61.0, 81.0, and 114.0 μL of the stock solution of **9**. The solvents in each vial were removed in vacuo. Then 600 μL of CCl_4/CD_3OD (20/80) was added to each vial. The samples were gently shaken for 1 h and then transferred to 14 separate NMR tubes. ^{1}H NMR spectra were recorded for each sample, and the chemical shifts of pyridyl protons of the guest were measured. Binding constants were determined by nonlinear least-squares curve fitting of the titration data.

Catalytic Epoxidation. CCl_4/MeOH was degassed by three freeze−pump−thaw cycles and stored under nitrogen. Analyses of reaction products were performed with GC and, if necessary, GC-MS. GC was performed on aliquots directly withdrawn from the reaction mixture. Authentic samples of epoxide products were purchased from Aldrich or synthesized using *m*-chloroperbenzoic acid. A typical procedure for the catalytic epoxidation is as follows. A 2 mL vial was charged with Fe(CFTPP)Cl (4.4 mg, 1.0 μmol) under nitrogen. A mixture of CCl_4 and MeOH (=90:10, 0.8 mL) was added via a syringe. The mixture was sonicated for 2 min at room temperature. Cyclohexene (**11**; 102 μmol), 3-cyclohexene-1-methanol (**14**; 102 μmol), and 3-cyclohexene-1,1-dimethanol (**15**; 102 μmol) were added. PhIO (4.5 mg, 20 μmol) was added under nitrogen. Dodecane (10 μmol) was added as an internal standard. The reaction products were analyzed by GC after 3 h.

Acknowledgment is made to the Center for Catalysis at Iowa State University for partial support of this research.

Supporting Information Available: Text giving synthetic procedures for **3** and **4**, figures giving the ^{1}H NMR spectra for compounds **3**, **4**, **2**, Zn(CFTPP), **7**, and **9**, and tables giving data on competetive epoxidation. This material is available free of charge via the Internet at http://pubs.acs.org.

OM060791Z

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