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A DMAP-functionalized oligocholate foldamer for solvent-responsive catalysis

Hongkwan Cho, Zhenqi Zhong, Yan Zhao *

Department of Chemistry, Iowa State University, Ames, IA 50011-3111, USA

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A hexameric cholate foldamer functionalized with a 4-dialkylaminopyridyl group displayed solvent-sensitive catalysis for the acetylation of alcohols. The catalyst folded in carbon tetrachloride containing a low percentage (<4%) of DMSO and unfolded as more DMSO was added. By increasing the effective concentration of the substrate near the catalytic group, the folded catalyst was more active than the unfolded catalyst toward small, hydrophilic alcohols. The longer and hydrophobic *n*-octanol, however, was more reactive in the presence of the unfolded catalyst. The highest selectivity (21:1) was observed for methanol/*n*-octanol with the folded oligocholate catalyst.

1. Introduction

The polarity, distribution of functional groups, and shape of the active site of an enzyme are tailored by nature for highly efficient catalysis and remarkable selectivity. Chemists have long been interested in creating ‘nanoreactors’ resembling enzyme active sites for similar purposes.[1–3] Recently, Rebek and co-workers controlled the regioselecticity of the ring opening of an epoxide by a carboxyl-functionalized deep cavitand.[4] Using self-assembled coordination cages, Fujita and co-workers obtained unusual cycloaddition products of arenes.[5] Warmuth and Makowiec found that the inner space of hemicarcerands had unusual abilities to stabilize reactive intermediates such as triplet phenylnitrene.[6] Ramamurthy and co-workers reported that guest-packing within a supramolecular capsule strongly influenced the photochemistry of ketones.[7] Although remarkable progress has been made, the nanoreactors in the literature were nearly all rigid structures,[1–7] whereas the active site of an enzyme is formed by the folding of a conformationally mobile peptide chain. An attractive feature of a folded construction is that both the reactivity and selectivity of enzymes can be tuned by the conformational change of the peptide chain.[8]

In recent years, foldamers have emerged as a fascinating class of synthetic molecules mimicking biomolecules in their conformational behavior.[9–11] Although numerous foldamers have been reported in the literature, foldamer-based catalysts are still rare.[12–15] Moore used his *m*-phenyleneethynylene oligomer as ‘molecular sieves’ to control the reactivity of methyl sulfonate toward a pyridyl group positioned in the middle of the foldamer.[12] The ultimate goal of the research is to take ideas from nature and develop highly selective synthetic catalysts that rival enzymes.[12d] More recently, Li and co-workers found that their aromatic amide foldamers could accelerate the hydrolysis of nitro-substituted anisole in aqueous solution.[13]

Our group synthesized oligocholate foldamers. With the amphiphilic repeat unit curved toward the hydrophilic face, the oligocholate easily curls into a helix when dissolved in nonpolar solvents (e.g., CCl_4 or hexane/ethyl acetate mixtures) containing a small amount of polar solvent (e.g., DMSO or small alcohol).[16] During folding, the inwardly facing polar NH/OH groups concentrate some polar solvent molecules from the bulk into the central cavity.[17] As shown by Figure 1, the driving force for folding is the preferential solvation of the cholate hydrophilic faces by the microphase-separated polar solvent. In this paper, we report a solvent-sensitive oligocholate catalyst. Notably, both the activity and selectivity of the foldamer catalyst can be tuned rationally as the catalyst folds and unfolds.[18,19]

2. Results and discussion

2.1. Design and synthesis of oligocholate catalyst

The central cavity of the folded oligocholate is about 1 nm in diameter and can bind hydrophilic guests. Importantly, the binding could be turned on and off by the folding and unfolding of the foldamer. In addition, the conformational change of the oligocholate is highly sensitive to the environment. Dramatic changes in the folding energy may be triggered by <0.5% change in the solvent

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* Corresponding author. Tel.: +1 515 294 5845; fax: +1 515 294 0105.
E-mail address: zhaoy@iastate.edu (Y. Zhao).

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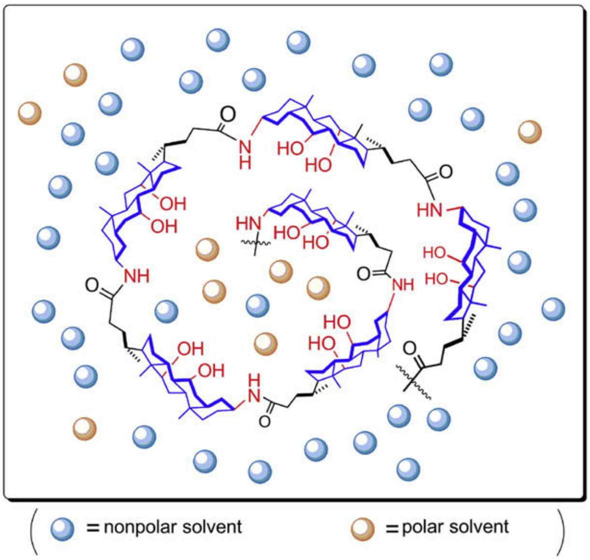


Figure 1. Schematic representation of the preferential solvation of a folded oligocholate.

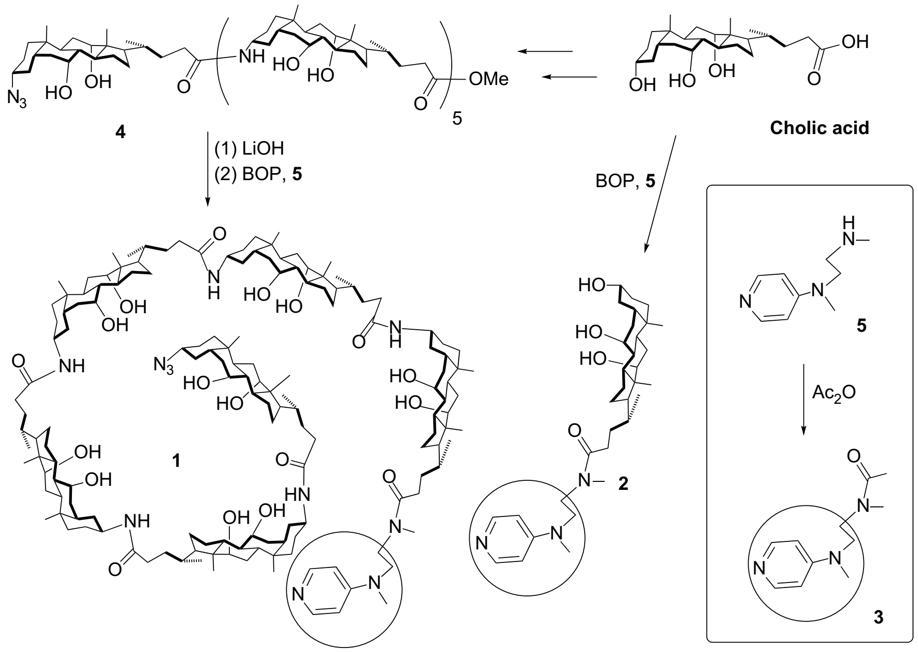
composition for the parent oligocholates.[16] These features make the oligocholates highly suitable for designing environmentally responsive catalysts.

Previously, it was found that oligocholates with ≥5 repeat units can fold and unfold cooperatively in appropriate solvents.[16] We thus designed foldamer catalyst **1**, with six cholate units and a 4-dialkylaminopyridine moiety at the chain end. The latter is an analogue of 4-dimethylaminopyridine (DMAP), a powerful catalyst for acyl transfer.[20] Transacylation is one of the most common reactions in organic chemistry. It is related to many important biological reactions (e.g., formation and hydrolysis of amide and phosphate ester). Although the reaction can be accelerated via a variety of mechanisms, nucleophilic catalysis by *N*,*N*-dimethylaminopyridine (DMAP)[20] or imidazole[21–23] is most amenable to the design of tunable foldamer catalysts. Our design is quite straightforward. A proven catalytic functionality is attached to the foldamer. As the oligocholate folds and unfolds, the microenvironment near the catalytic moiety is altered. The question is whether the conformational change of the oligocholate (which can be controlled rationally) can influence the *activity* and *selectivity* of the catalyst. To answer this question, we also prepared catalysts **2** and **3**. Having one or no cholate, they cannot fold. Because the structural difference in **1**–**3** is about nine bonds away from the pyridyl nitrogen and five (σ) bonds away from the amino nitrogen on the pyridine, the structural difference is unlikely to perturb the catalytic pyridyl group electronically.

Syntheses of the catalysts are shown in Scheme 1. Cholate hexamer **4** was prepared from cholic acid according to the previously reported procedures.[16] The amine-terminated pyridyl derivative (**5**) was obtained by treating 4-chloropyridine with an excess of *N*,*N*′-dimethylethylenediamine.[24] Compound **4** was then hydrolyzed with LiOH, and the resulting acid was coupled to **5** using benzotrazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) in anhydrous DMF. Similar amide coupling between cholic acid and **5** afforded monocholate catalyst **2**. Control catalyst **3** was prepared by treating **5** with acetic anhydride.

2.2. Effect of conformational change on catalytic activity

A wide variety of acyl-donors (acid chloride, anhydride, activated esters such as *p*-nitrophenyl acetate) and acceptors (water, alcohol, and amine) with different reactivity are available. A proper balance in the reactivity of the acyl-donor and acceptor is needed for the oligocholate to impact the reaction. A highly reactive donor–acceptor pair has a large background reaction, making the participation of the pyridyl group (and in turn the oligocholate) difficult. Too sluggish donor–acceptor pairs are not good either, as it may be difficult to detect the catalysis. We choose alcohols as the acyl-acceptors. Their hydrophilicity and reactivity are easily tuned by the alkyl group. Small, hydrophilic alcohols can enter the hydrophilic cavity of the oligocholate easily but large, hydrophobic ones cannot (Fig. 1). Even though the catalytic pyridyl group may not stay within



Scheme 1. Synthesis of catalysts **1**–**3**.

the cavity, bringing the catalytic group and the acyl-acceptor into proximity should facilitate the reaction.

We initially employed *p*-nitrophenyl acetate, a popular acyl-donor, and studied the transfer of acetyl to methanol (i.e., methanolysis). Although DMAP was found to catalyze the reaction in neat methanol, it was completely ineffective in solvent mixtures (e.g., 5% MeOH/CCl_4) amenable to the folding of the oligocholates. A more reactive acyl-donor was thus needed, and acetic anhydride proved suitable for our purpose.

To understand the effect of the conformation of **1** on its activity, we first studied acetylation of methanol under pseudo-first order conditions. Acetic anhydride (3 mM) was mixed with a large excess (0.5 vol % or ~120 mM) of deuterated methanol in a mixture of DMSO-d_6 and CCl_4. The concentration of the catalyst was 20 μM, <1% of that of the acetic anhydride. We chose such a concentration partly because a fluorescently labeled heptacholate showed no sign of aggregation at similar concentrations in 2% DMSO/CCl_4.[16] In the current investigation, the most nonpolar (i.e., the most 'aggregation-prone') solvent system contains a similar amount of polar solvent (e.g., 0.5% MeOH+1.5% DMSO). Since the tendency of aggregation increases with the chain length, the hexameric cholate catalyst (**1**) is unlikely to aggregate under our reaction conditions.

Diisopropylethylamine (DIPEA, 20 mM), a hindered organic base, was also included in the reaction mixture to neutralize the acetic acid formed during the reaction. This procedure is to avoid protonation and deactivation of the catalyst. A preliminary experiment shows that this hindered base is not able to promote the reaction to any significant degree, possibly because of its low nucleophilicity. For example, whereas the reaction between acetic anhydride and methanol in 5% DMSO/CCl_4 was near completion within 60 min when catalyzed by **1** or **2**, it did not proceed at all with DIPEA alone (Fig. 1S, Supplementary data).[25]

We monitored the progress of the reaction by ^{1}H NMR spectroscopy. Table 1 summarizes the rate constants obtained from linear curve-fitting. All the *R* factors were at least 0.99 and linearity was maintained even at high conversion (e.g., 80%).[26] The error in the rate constants was estimated to be about 10–20%. For easier comparison, we kept the concentration of methanol constant. As DMSO was increased from 1.5 to 19.5 vol % in the reaction mixture, **1** is expected to go from the folded to the unfolded state,[16,17] whereas monocholate **2** and control **3** are unable to do so.

At the nonpolar end of the solvent mixture, **1** is clearly a more efficient catalyst than control **3**. In 1.5 and 3.5% DMSO/CCl_4, the acetylation of methanol catalyzed by **1** is 2.6 ($=k_1/k_3$) times as fast as the reaction catalyzed by **3** (Table 1, entries 1 and 2). As the amount of DMSO increases, the hexameric catalyst loses its lead. The k_1/k_3 ratio is only 1.6 in 7.5% DMSO and drops to 1.0 in 19.5% DMSO.

The kinetic data is in line with the folding/unfolding of **1**. In the folded state, the catalyst is able to concentrate methanol into its hydrophilic cavity (see below for further discussion). As mentioned earlier, methanol is completely unreactive toward acetic anhydride within the time frame (0.5–2 h) of our experiments without the DMAP catalyst. Hence, acetylation of methanol can only happen *after* acetic anhydride reacts with the pyridyl group. The higher activity of the folded **1** in comparison to **2** or **3** supports a higher effective concentration of methanol near the catalytic group in the former.

Previously, UV–vis spectroscopy indicated that a (NBD-labeled) cholate heptamer was completely unfolded with >4% DMSO in CCl_4.[15] In the acetylation, however, hexacholate **1** shows more efficient catalysis than monocholate **2** in 7.5% DMSO/CCl_4 (Table 1, entry 4), a mixture in which **1** should be unfolded. It is possible that a small percentage of folded catalyst still exists in 7.5% DMSO/CCl_4 and is responsible for the enhanced catalysis. It is also possible that the same unfolding/unfolding equilibrium affects the fluorescent label (on the heptacholate) and the pyridyl (on **1**) differently. Even though the solvent effects on the spectroscopic or catalytic properties of these labeled oligocholates both derive from the same folding/unfolding equilibrium, there is no reason for these effects to be synchronous or have the same sensitivity.[16] According to our earlier work in cholate-derived molecular baskets, inhomogeneity in solvent distribution around the cholates often precedes large-scale conformational change of the entire molecule.[27] It is thus possible that an increased local concentration of MeOH near the pyridyl group could occur in **1** before its folding can be detected by a spectroscopic method. Regardless of the exact reason for the enhanced catalysis with **1** in 7.5% DMSO/CCl_4, further addition of DMSO diminishes the effect. By the time 15–19% DMSO is added to the reaction mixture, all three catalysts have identical activity (Table 1, entries 6 and 7).

Table 1

Rate constants for the reaction between methanol and acetic anhydride at 20 °C in DMSO/CCl_4 mixtures[a]

Entry	% CD_3OD[b]	% DMSO[c]	Catalyst	k (min^{-1})[d]	k_1/k_3[e] (k_2/k_3)[e]
1	0.5	1.5	1	1.0×10^{-2}	2.6 (1.4)
			2	5.6×10^{-3}	
			3	3.9×10^{-3}	
2	0.5	3.5	1	8.3×10^{-3}	2.6 (1.4)
			2	4.6×10^{-3}	
			3	3.2×10^{-3}	
3	0.5	5.5	1	6.4×10^{-3}	1.7 (1.2)
			2	4.4×10^{-3}	
			3	3.8×10^{-3}	
4	0.5	7.5	1	5.4×10^{-3}	1.6 (1.1)
			2	3.4×10^{-3}	
			3	3.3×10^{-3}	
5	0.5	11.5	1	2.4×10^{-3}	1.2 (1.1)
			2	2.2×10^{-3}	
			3	2.1×10^{-3}	
6	0.5	15.5	1	2.1×10^{-3}	1.1 (1.0)
			2	2.0×10^{-3}	
			3	1.9×10^{-3}	
7	0.5	19.5	1	1.7×10^{-3}	1.0 (0.9)
			2	1.5×10^{-3}	
			3	1.7×10^{-3}	

[a] $[Ac_2O]=3.0$ mM, [DIPEA]=20.0 mM, [catalyst]=20 μM.

[b] Volume percentage of methanol in the reaction mixture, corresponding to a concentration of 120 mM.

[c] Volume percentage of DMSO-d_6 added to control the folding/unfolding of the oligocholate foldamer.

[d] The error for the rate constants determined by ^{1}H NMR spectroscopy was estimated to be 10–20%.

[e] k_1, k_2, and k_3 are the rate constants for the reaction catalyzed by **1**, **2**, and **3**, respectively.

Although the trend in the rate constants is consistent with the folding/unfolding of **1**, the 2.6-fold improvement over the control does not seem very impressive. Nevertheless, DMAP derivatives are extremely powerful transacylating catalysts.[20] Speeding up an inefficient catalyst is trivial but doing so to a highly efficient catalyst is not as easy. Another reason for the small improvement in catalysis is probably the co-solvent DMSO. Our previous work shows that the folding of an oligocholate is favored by larger polar solvents within a homologous series,[17] as fewer of such polar solvent molecules can fill the nanocavity to provide solvation for the inwardly facing polar groups (see Fig. 1). Separation of the polar solvent from the bulk into the foldamer cavity is needed for folding, but demixing of solvents itself costs free energy in the meanwhile. In the case of larger polar solvents, fewer solvent molecules need to be demixed from CCl_4 and the cost of free energy for the folding is lower. Although DMSO and methanol have different functional groups, the former should be favored by the hydrophilic cavity of **1** due to its larger size and stronger hydrogen-bonding ability—a result confirmed in both foldamer[16] and nonfoldamer[27] oligocholates. If methanol struggles in its competition for the internal cavity, its effective concentration near the pyridyl group will be limited and the resulting catalysis will also be limited.[28] Thus, the 2.6-fold improvement of catalysis in **1** is quite a reasonable result.

2.3. Effect of conformational change on catalyst's selectivity

The exact position of the catalytic pyridyl group is unclear with respect to the nanocavity of **1**, although one could speculate that its high polarity may favor its location within the cavity. When a substrate approaches the catalytic group, even if the pyridyl is outside the cavity, the local pool of polar solvent should 'repel' a hydrophobic substrate. Therefore, we expect, other than the activity of the catalyst, its selectivity to be affected by the folding/unfolding equilibrium as well.

To test this hypothesis, we studied the second-order kinetics of the acetylation of several alcohols (Table 2). Although DMAP derivatives are particularly powerful for the acylation of tertiary alcohols,[20] we used only primary alcohols to avoid large differences in the inherent reactivity among the substrates. Additionally, small, hydrophilic alcohols (e.g., methanol, ethanol) are preferred by the oligocholates and will most likely experience the largest folding/unfolding effect. Second-order reactions were necessary because different alcohols have different polarity and molecular weight. Neither the folding/unfolding equilibrium of the catalyst nor the concentration of the substrate can be kept constant if the same volume percentage of different alcohols was used as in the first set of experiments. When the alcohol was kept at a concentration of 20 mM (<0.1 vol %), the folding of **1** is largely controlled by the percentage of DMSO.

Catalyst **1** is folded in 1.5% DMSO. As mentioned earlier, at 20 μM of concentration, aggregation of the catalyst should not be a concern.[16] When the different alcohols are compared, methanol is by far the most reactive substrate, acetylated 21 times faster than the hydrophobic *n*-octanol (Table 2, k_{rel}, entries 1 and 5) in 1.5% DMSO/CCl_4. The other small alcohols (C2–C4) have fairly similar reactivity, with the rate constants 2–4 times larger than that of *n*-octanol. On the other hand, the difference in the reactivity is much smaller for the alcohols in 20% DMSO. In the latter case, methanol is still the most reactive one, but the rate constant is only 2.6 times of that of *n*-octanol. Clearly, the inherent difference in the reactivity of octanol/methanol only accounts for a fraction of the 21-fold increase in reaction rate when the catalyst is folded. For the unfolded catalyst (in 20% DMSO), ethanol, propanol, *n*-butanol, and *n*-octanol all have very similar rate constants, essentially within the experimental error of the NMR kinetic methods. Therefore, the accessibility of the different alcohols to the pyridyl group is largely the same in the unfolded catalyst. The higher k_{rel} for methanol in 20% DMSO most likely results from its higher inherent reactivity.

Table 2
Rate constants (M^{-1} min^{-1}) for the reaction between different alcohols and acetic anhydride at 20 °C in DMSO/CCl_4 mixtures[a]

Entry	Alcohol	k (k_{rel}) in 1.5% DMSO/CCl_4[b,c]	k (k_{rel}) in 20% DMSO/CCl_4[b,c]	k_{fold}/k_{unfold}[d]
1	MeOH	9.3×10^{-2} (21)	2.2×10^{-2} (2.6)	4.3
2	EtOH	1.5×10^{-2} (3.5)	8.3×10^{-3} (1.0)	1.9
3	PrOH	1.1×10^{-2} (2.4)	6.4×10^{-3} (0.8)	1.7
4	*n*-BuOH	1.1×10^{-2} (2.5)	5.4×10^{-3} (0.7)	2.1
5	*n*-OctOH	4.4×10^{-3} (1.0)	8.2×10^{-3} (1.0)	0.5

[a] [Alcohol]=[Ac_2O]=[DIPEA]=20.0 mM, [catalyst]=20 μM.

[b] Volume percentage of DMSO-d_6 added to control the folding/unfolding of the oligocholate foldamer.

[c] The error for the rate constants determined by ^1H NMR spectroscopy was estimated to be 10–20%.

[d] k_{fold} and k_{unfold} are the rate constants for the reactions catalyzed by **1** in 1.5 and 20% DMSO, respectively.

When the rate constants of the same substrate in 1.5 and 20% DMSO are compared, the k_{fold}/k_{unfold} ratio factors out the inherent reactivity of the substrate and is an indicator for the effect of the conformational change of the catalyst on the alcohol (Table 2). Methanol benefits most from the folding of the catalyst, with the k_{fold}/k_{unfold} ratio of 4.3. The C2–C4 alcohols are mildly preferred by the folded catalyst, with $k_{fold}/k_{unfold} \approx 2$. Hence, nearly all the alcohols are more reactive with the folded catalyst, with the only exception being *n*-octanol—its acetylation is faster with the *unfolded* catalyst by a factor of 2. This result confirms our earlier hypothesis. In the folded catalyst, the pyridyl group is near a tiny pool of polar solvent (i.e., DMSO). Although the catalytic group is not necessarily located within the polar pool, the polar solvent is able to 'repel' the hydrophobic *n*-octanol to reduce its reactivity, but, at the same time, promotes the reaction of methanol. This effect is similar to what was observed in our cholate-derived porphyrin catalyst.[19a] In the porphyrin catalyst, the catalytic center was enclosed by eight cholate groups, and the local pool of polar solvent was able to distinguish two substrates different by one hydroxyl group in their reactivity by a 10:1 ratio.

Our previous work indicates that, for C1–C4 alcohols, the larger alcohols are more beneficial to the folded oligocholates than smaller ones.[17] Does this earlier conclusion suggest that the larger ethanol or propanol should enter the nanocavity of the folded **1** more easily than methanol? To answer this question, one has to remember that DMSO is the strongest 'occupant' of the hydrophilic cavity of **1** in the reaction mixture because of its stronger hydrogen-bonding ability, its larger size, and its higher concentration (i.e., 1.5%) compared to that of the alcohol (<0.1%). If the alcohols cannot easily displace DMSO from the nanocavity, the most efficient way of increasing their effective concentration near the catalyst is to associate with the DMSO molecules near the nanocavity of the catalyst. Methanol undoubtedly should win in such a competition because of its highest hydrophilicity among the alcohols.

3. Conclusions

Conformational regulation of catalysis is a skill mastered by nature in enzymes but only recently became available to chemists as we started designing conformational mimics of proteins (i.e., foldamers).[9,10] In this paper, we describe a catalytic oligocholate that has a hydrophilic nanocavity upon folding. The folded catalyst is more active toward hydrophilic substrates by increasing their local concentration near the catalytic group. Reasonably high selectivity (methanol/*n*-octanol=21:1 for the folded **1**) is achieved in the current system, although the foldamer catalyst only shows moderate (2.6×) improvement over the control (**3**) in the acetylation of methanol. The selectivity demonstrated in this work is similar to what was achieved with the *m*-PE foldamers by Moore.[12c] Therefore, 'molecular sieving' (i.e., selecting substrates based on their sizes) may not only be achieved by placing the catalytic group on the internal wall of the foldamer as in Moore's work,[12] but also by a microphase-separated solvent pool as in this work.

Many factors play roles in the efficiency of the oligocholate–DMAP catalyst, including the inherent activity of the catalytic group, the competition between the substrate and the solvents, and the reactivity of the substrate. Optimizing these factors is important if more efficient catalysis is desired. Although far from ideal, the oligocholate catalyst has demonstrated that a rational design of tunable catalysts can be easily achieved with synthetic foldamers.

4. Experimental

4.1. General

Anhydrous tetrahydrofuan (THF) and methylene chloride were dried by passage through a column of activated alumina under compressed nitrogen. Cholic acid was crystallized from 95% ethanol. Methanol, hexanes, and ethyl acetate were of HPLC grade and were purchased from Fisher Scientific. All other reagents and solvents were of A.C.S. certified grade or higher, and were used as received from commercial suppliers. All glassware and syringes were dried in an oven at least overnight prior to use. Routine ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 or on a Varian VXR-400 spectrometer. Kinetic ^{1}H NMR study was conducted with the Bruker DRX-400. MALDI-TOF mass spectrometry was recorded on a Thermobioanalysis Dynamo mass spectrometer. HRMS mass spectrometry was recorded on an MS 50 mass spectrometer.

4.2. Preparation of the catalysts

*4.2.1. Compound **5***

This compound was synthesized according to literature procedure.[20] A mixture of 4-chloropyridine hydrochloride (510 mg, 3.40 mmol), *N*,*N*′-dimethyl-1,2-ethanediamine (750 mg, 8.50 mmol), and sodium bicarbonate (857 mg, 10.2 mmol) in isoamyl alcohol (100 mL) was heated to reflux for 48 h. The mixture was concentrated by rotary evaporation and the residue was purified by column chromatography over silica gel using CH_2Cl_2/MeOH (10:1) and MeOH/TEA (50:1) to give a yellowish oil (420 mg, 75%); δ_H (400 MHz, $CDCl_3$) 2.44 (s, 3H), 2.78 (2H, t, *J* 6.6), 2.98 (3H, s), 3.46 (2H, t, *J* 6.6), 6.50 (2H, dd, *J* 1.6) and 5.0, 8.17 (2H, dd, *J* 1.6 and 5.0).

*4.2.2. Compound **1***

The synthesis of oligocholates (including hexamer **4**) and the hydrolysis of the ester end group were reported previously.[16] The acid derivative of **4** (165 mg, 0.07 mmol), compound **5** (23 mg, 0.14 mmol), BOP (39 mg, 0.0875 mmol), and DIPEA (54 mg, 0.42 mmol) were dissolved in anhydrous DMF (3 mL). The mixture was stirred under N_2 at 50 °C for 8 h. The crude product was obtained by precipitation into acetonitrile followed by column chromatography over silica gel (130 mg, 74%); δ_H (400 MHz, $CDCl_3$/CD_3OD=1:1) 0.58–0.70 (18H, m), 0.80–2.32 (180H, m), 3.12–2.94 (6H, m), 3.15 (1H, m), 3.42–3.65 (9H, m), 3.78 (6H, m), 3.85–3.98 (6H, m), 7.58–7.80 (2H, m), 8.02–8.15 (2H, m); δ_C (100 MHz, $CDCl_3$/CD_3OD=1:1) 12.40, 12.45, 17.15, 17.21, 17.3, 17.8, 22.59, 22.64, 23.3, 26.6, 26.7, 27.4, 27.7, 28.3, 29.8, 30.6, 31.1, 31.9, 32.2, 32.9, 33.60, 33.65, 34.7, 34.9, 35.1, 35.6, 35.7, 35.8, 36.0, 36.3, 36.8, 37.7, 38.8, 38.9, 39.5, 39.6, 41.8, 41.9, 42.1, 45.7, 46.5, 47.1, 49.5, 49.7, 49.8, 57.6, 61.7, 68.0, 68.2, 68.4, 77.9, 73.1, 107.0, 128.9, 131.3, 145.7, 155.5, 174.4, 174.5, 175.3; *m*/*z* (MALDI-TOFMS) (*m*/*z*): 2516 ($[M+H_3O-N_2]^+$. $C_{153}H_{250}N_9O_{19}$ requires 2520).

*4.2.3. Compound **2***

Cholic acid (139 mg, 0.34 mmol), compound **3** (51 mg, 0.31 mmol), BOP (150 mg, 0.34 mmol), and 1-hydroxybenzotriazole hydrate (HOBt, 46 mg, 0.34 mmol) were dissolved in anhydrous DMF (5 mL). DIPEA (0.12 mL, 1.24 mmol) was added. The reaction mixture was stirred at 50 °C under N_2. After 20 h, solvent was removed by rotary evaporation and the residue was purified by column chromatography over silica gel using CH_2Cl_2/MeOH (10:1) and MeOH/TEA (80:1) as the eluents to give an off-white powder (155 mg, 90%); δ_H (400 MHz, CD_3OD) 0.70 (s, 2.1H), 0.65 and 0.70 (2×s, 3H), 0.84–2.37 (m, 33H), 2.98 and 3.04 (2×s, 3H), 3.03 (s, 3H), 3.37 (m, 1H), 3.72–3.54 (m, 4H), 3.79 (br, 1H), 3.89 and 3.94 (2×br, 1H), 6.71 (br, 2H), 8.07 (br, 2H); δ_C (100 MHz, CD_3OD) 13.1, 13.2, 17.9, 23.3, 24.4, 27.9, 28.0, 28.8, 28.9, 29.7, 31.3, 32.4, 34.3, 36.0, 36.6, 37.0, 37.4, 37.8, 39.1, 40.6, 41.2, 43.0, 43.1, 43.3, 47.5, 47.6, 47.8, 47.9, 50.3, 69.1, 73.0, 74.0, 74.1, 149.5, 156.0, 176.4, 176.8; *m*/*z* (HRMS) 555.4036 (M^+, $C_{34}H_{55}N_2O_4$ requires 555.4025).

*4.2.4. Compound **3***

Compound **5** (30 mg, 0.18 mmol) and DIPEA (0.050 mL, 0.55 mmol) were dissolved in CH_2Cl_2 (3 mL). Acetic anhydride (0.026 mL, 0.27 mmol) was slowly added. After 6 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL), and water (2×10 mL). The organic phase was dried over $MgSO_4$, concentrated by rotary evaporation to give a colorless oil (20 mg, 53%); δ_H (400 MHz, CD_3OD) 1.91 and 1.95 (2×s, 3H), 2.94 and 3.00 (2×s, 6H), 3.52–3.67 (m, 4H), 6.70 (br, 2H), 8.01 (br, 2H); δ_C (100 MHz, $CDCl_3$/CD_3OD=4:1) 20.6, 21.4, 29.6, 33.7, 37.4, 37.6, 38.3, 45.6, 48.0, 48.3, 49.3, 148.7, 149.2, 153.3, 154.0, 171.4, 172.1; *m*/*z* (HRMS) 207.1374 (M^+, $C_{11}H_{17}N_3O$ requires 207.1372).

4.2.5. Kinetic measurement by ^{1}H NMR spectroscopy

A typical procedure for the ^{1}H NMR kinetic experiment is as follows. Stock solutions of compound **1** in DMSO-d_6 (2.0×10^{-3} M), DIPEA in CCl_4 (1.0×10^{-1} M), and Ac_2O in CCl_4 (6.0×10^{-2} M) were prepared. Aliquots of the stock solutions of **1** (10.0 μL) and DIPEA (200 μL) were added to an NMR tube with Hamilton Gastight syringes. DMSO-d_6 (5.0 μL) and CCl_4 were added to give a total volume of 950 μL. Upon addition of the Ac_2O solution (50 μL), the reaction was followed by ^{1}H NMR spectroscopy. The methyl protons of the acetic anhydride and the product were integrated for the kinetic analysis. The proton peaks of DIPEA were used as the internal reference. For the samples containing 1.5 and 3.5% of DMSO-d_6, a sealed capillary tube filled with DMSO-d_6 was placed into the NMR tube for shimming.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.018.

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