Substrate-Specific Amidation of Carboxylic Acids in a Liquid−Liquid Two-Phase System Using Cyclodextrins as Inverse Phase-Transfer Catalysts

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A novel system for substrate-specific activation of carboxylic acids leading to the formation of carboxamides has been developed in our laboratory. A combination of a water-soluble dehydrocondensing agent, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), and an inverse phase-transfer catalyst (IPTC) (hydroxypropyl)cyclodextrin (HP-β-CD), in a water/ether biphasic solvent system was found to be most effective. A lipophilic carboxylic acid with a strong affinity for the cavity of HP-β-CD can be selectively transferred to the aqueous phase and predominantly reacts with DMT-MM, dissolving in the aqueous phase. The substrate specificity was similar to that observed with a complex artificial enzyme based on CD.

Introduction

Many efforts have been made to use host compounds for various types of selective reactions,[1,2] which are of great importance in organic synthesis because they offer a highly effective way to synthesize desired compounds. Cyclodextrin (CD) derivatives are among the most general and well-studied of host compounds.[1] Since a major driving force for the formation of inclusion complexes between CD and lipophilic organic compounds is the hydrophobic effect, which is most effectively enhanced in water,[3] reactions in which CDs are used as host molecules should be compatible with water. Therefore, it would seem difficult to apply CDs to reactions such as dehydrocondensation, that are conducted essentially under dry conditions. The polyhydroxylated nature of CDs presents other limitations to both their selective chemical modification to introduce a special functionality corresponding to a reaction site and purification of the resulting modified CDs.

Recently, we developed a new condensing agent, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), which enables us to carry out activation of carboxylic acids in protic solvents such as water, MeOH, and EtOH as well as various aprotic solvents.[4] In a novel application of these agents to a CD, we first developed a CD-based artificial acyltransferase that converts 4-substituted benzoic acids into amides in a substrate-specific manner in an aqueous solvent.[5] In this model, the substrate binding site (CD) and the reaction site (triazino group) must be linked to bring the substrate (carboxylic acid) into close proximity with the triazino group to both accelerate the reaction and promote substrate specificity. Indeed, control reactions using a combination of 2,3,6-trimethylated β-CD and a triazino group that are totally separated resulted in the complete loss of the selectivity. In general, the use of CDs as artificial enzymes entails tedious chemical modification of CDs. If commercially available CDs with a simple structure could be used directly, the substrate-specific dehydrocondensation would become more practical. To that end, we developed a new system for substrate-selective amidation of carboxylic acids using a combination of DMT-MM and a simple, commercially available CD under inverse phase-transfer conditions in which the binding site and the reaction site were completely separated from each other.

Because water-soluble DMT-MM is almost insoluble in less polar organic solvents such as diethyl ether, EtOAc, and CH_2Cl_2,[6] it should distribute itself exclusively to the aqueous phase when dissolved in two immiscible liquid phases consisting of water and organic solvents. When a mixture composed of several kinds of carboxylic acids and an amine is added to the biphasic system, a carboxylic acid that is predominantly dissolved in an aqueous phase should be activated by DMT-MM faster than one in an organic phase, because a homogeneous reaction should proceed faster than a heterogeneous one. The resulting acyloxytriazines, in turn, undergo aminolysis to give carboxamides. Thus, the substrate selectivity should depend on the distribution of the substrates between the two liquid phases and, in general, hydrophilic carboxylic acids should be selectively activated. By the same reasoning, both the selectivity and the yield can be expected to be poor when all carboxylic acids are lipophilic. On the other hand, if a particular lipo-

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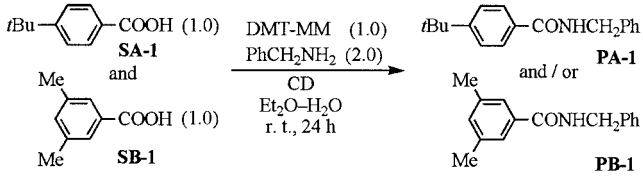
philic carboxylic acid has a strong affinity for a CD cavity and can form a stable inclusion complex in water, that carboxylic acid can be selectively transferred to the aqueous phase by addition of the appropriate CD. The carboxylic acid transferred is now in the same phase as the activating agent, DMT-MM, and should be the acid that is predominantly activated. On the basis of this concept, we have developed a novel system to attain a substrate-selective amidation of carboxylic acids using a simple CD as an inverse phase-transfer catalyst (IPTC).[7,8]

Results and Discussion

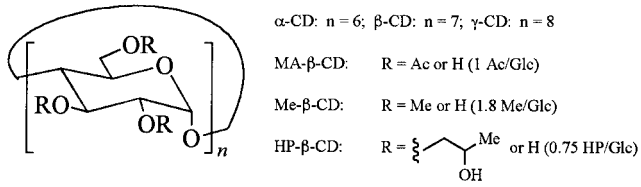
As a preliminary study, we examined the competitive reaction of 4-*tert*-butylbenzoic acid (**SA-1**) and 3,5-dimethylbenzoic acid (**SB-1**) with benzylamine in a biphasic system in the presence of a variety of inexpensive and readily available CDs. The former acid, **SA-1**, forms a stable inclusion complex with CDs, whereas the complex with the latter, **SB-1**, is too unstable to allow the determination of its dissociation constant by UV titration.[5] Accordingly, when both acids are dissolved in the appropriate organic phase, **SA-1** can be expected to selectively transfer to the aqueous phase by the formation of an inclusion complex with CDs, where it then predominantly undergoes coupling with DMT-MM dissolved in water. The resulting activated ester (acyloxytriazine) in turn couples with an amine to give a hydrophobic amide, which transfers to the organic phase. The results are summarized in Table 1. Experiments in which randomly methylated β-CD (Me-β-CD) was used as an IPTC indicated that Et_2O was the most suitable organic phase among the organic solvents (Et_2O, EtOAc and $CHCl_3$) immiscible with water (Runs 1−6).[9] When the reaction in Et_2O-H_2O was carried out in the absence of CDs, the amide arising from **SB-1** was the major product, as indicated by the ratio 69:31, whereas the amount of amide arising from **SA-1** increased with the addition of every kind of CD examined (1 equivalent, Runs 5−10). In particular, the ratio of the products was inverted when β-CD derivatives were used.[10] The best result was obtained when hydroxypropyl-β-CD (HP-β-CD) was used, in which case the product ratio was 73:27 (**PA-1**/**PB-1**). Decreasing the amount of HP-β-CD resulted in a decrease in selectivity whereas increasing the CD up to three equivalents did not improve the selectivity at all (Runs 11−14). Although it is not clear why HP-β-CD gives the best result, the selectivity may relate to the water-solubility of the CDs. In spite of the heterogeneous conditions, the stirring rate did not affect selectivity in the present system.

Table 1. Effect of CDs on the selectivity in a liquid−liquid biphasic system



Run	CD[a]	Equiv. of CD	Organic phase	Yield	Relative ratio **PA-1** : **PB-1**	Water solubility of CDs (g/100 mL)[b]
1[c]	none	—	AcOEt	46%	35 : 65	
2	Me-β-CD	1	AcOEt	60%	65 : 35	>150 g
3[c]	none	—	$CHCl_3$	58%	51 : 49	
4[d]	Me-β-CD	1	$CHCl_3$	59%	51 : 49	
5	none	—	Et_2O	77%	31 : 69	
6	Me-β-CD	1	Et_2O	84%	70 : 30	
7	α-CD	1	Et_2O	69%	38 : 62	14.5 g
8	γ-CD	1	Et_2O	67%	42 : 58	23 g
9	MA-β-CD	1	Et_2O	83%	64 : 36	>200 g
10	HP-β-CD	1	Et_2O	82%	73 : 27	>200 g
11	HP-β-CD	0.1	Et_2O	73%	45 : 55	
12	HP-β-CD	0.5	Et_2O	75%	65 : 35	
13	HP-β-CD	2	Et_2O	84%	76 : 24	
14	HP-β-CD	3	Et_2O	83%	74 : 26	

[a]



[b] Quoted from the catalog of Wacker Chemie GmbH. [c] Reaction time was 5 h. [d] Reaction time was 3 h.

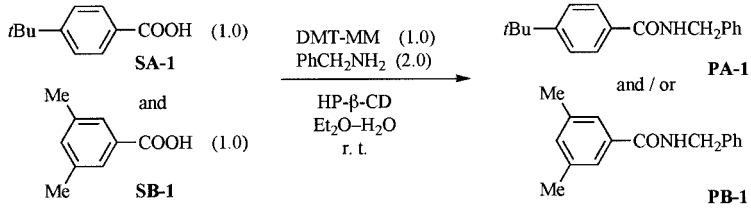
Since the observed selectivity seems lower than that expected on the basis of the affinity of **SA-1** for HP-β-CD,[11] we hypothesized that an alternative route responsible for decreasing the selectivity could be involved. Transfer of carboxylic acids to the aqueous phase by formation of ionized salts (ammonium carboxylate) with the amine, independent of the interaction with CD, seemed most likely. For that reason, we attempted to depress such transfer by (1) addition of NaCl to decrease the solubility of organic compounds in water by a salting-out effect, (2) lowering the substrate concentration of the organic phase by increasing the volume of Et_2O to shift the distribution equilibrium of the substrate to the organic phase, and (3) slow addition of an amine with a syringe pump to depress the amount of water-soluble ammonium carboxylates. As shown in Table 2, these adjustments improved the selectivity; the best selectivity was attained with a combination of all of the procedures (Run 5). The acceleration for **SA-1**, which is expressed by the relative proportional increase in the product ratio with respect to that obtained in the control experiment (Run 1), $(\textbf{PA-1/PB-1})_{rxn}/(\textbf{PA-1/PB-1})_{ctrl}$, was up to 30 times under these conditions with one equivalent of HP-β-CD. Furthermore, under these optimized conditions, we observed an acceleration of 35 times with 0.5 equivalents and over 22 times with a catalytic amount (0.1 equivalents) of HP-β-CD (Runs 8, 10).

In general, reactions in which host compounds are used suffer from product inhibition because the products still possess a high affinity to the host.[12] In our case, no significant decrease in the selectivity was observed when the competitive reaction was carried out in the presence of an equimolar amount of **PA-1** (Table 2, Run 6). This may indicate that the hydrophobic amide that is produced is almost insoluble in water and thus should exclusively stay in the organic phase, whereas the starting carboxylic acid (**SA-1**) complexed with the CD can be dissolved to some extent in the aqueous phase by forming a carboxylate ion.[13] Hydrogen bonding between hydroxy group(s) of HP-β-CD and the carboxyl group (or carboxylate) may also be responsible for the stabilization of the inclusion complex. The very small dissociation constant[11] of the inclusion complex of **SA-1** with HP-β-CD compared with that (3.1 mM) of **SA-1** with 2,3,6-trimethylated β-CD may indicate a special interaction in the former complex. On the basis of the optimum conditions obtained from the experiments in Table 2, we examined competitive reactions of substrates with and without affinity for HP-β-CD. As shown in Table 3, carboxylic acids with a high affinity for HP-β-CD were converted into amides with high selectivity by the addition of only 0.5 equivalents of HP-β-CD into the biphasic system.

It is often troublesome to separate a mixture of compounds whose polarity and chemical reactivity are similar to each other. By using the present method, the compound with the highest affinity for a given CD can be selectively converted into the amide from a mixture consisting of several kinds of organic acids. The amide produced can be easily purified without using chromatography, because its chemical properties are considerably different from other remaining starting materials. For example, when an equimolar mixture of four kinds of organic acids (**SA-1** and **SB-1**, **2**, and **3**) was allowed to react with DMT-MM in the liquid−liquid biphasic system, all the amides were formed to some extent in the absence of a CD, though their product/substrate ratios varied. On the other hand, the amide derived from the carboxylic acid with the highest affinity for HP-β-CD, **PA-1**, became the major product upon addition of 0.2 equivalents of the CD (Figure 1).

In general, it is essential that the substrate recognition site and the reactive site work cooperatively in order for a reaction to proceed in a substrate-specific manner under

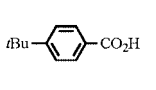
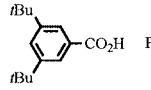
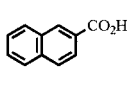
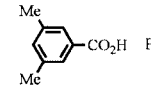
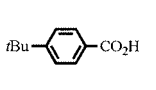
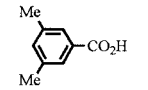
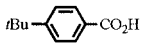
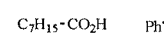
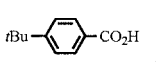
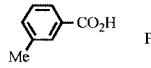
Table 2. Attempt to improve the substrate selectivity in Et_2O/water



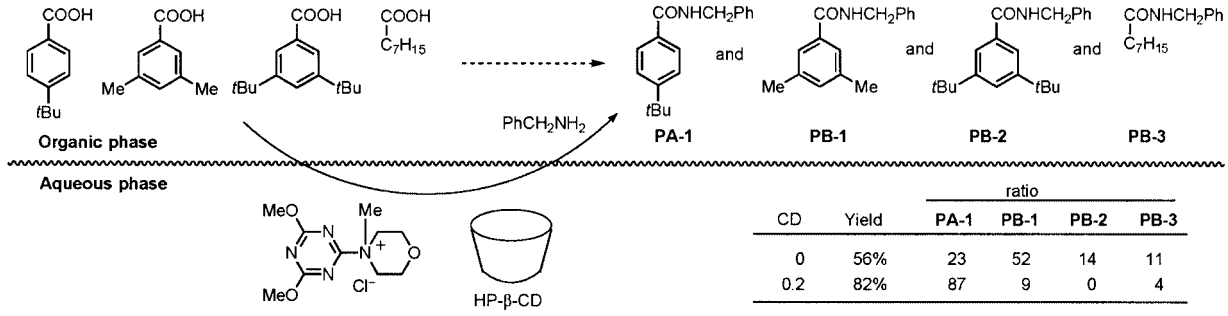
Run	CD (equiv)	NaCl (M)	Solvent ratio Et_2O : H_2O	Method[a]	Yield (%)	Ratio (PA-1 : PB-1)	Ratio PA-1/PB-1	Relative rate
1	none	0	1 : 1	A	77	31 : 69	0.45	1.0
2	1	0	1 : 1	A	82	73 : 27	2.7	6.0
3	1	5	1 : 1	A	80	78 : 22	3.5	7.9
4	1	5	4 : 1	A	78	80 : 20	4.0	8.9
5	1	5	4 : 1	B	83	93 : 7	13.3	29.6
6[b]	1	5	4 : 1	B	51	90 : 10	9.0	20.0
7	1	0	4 : 1	B	77	87 : 13	6.7	14.9
8	0.5	5	8 : 1	C	79	94 : 6	15.7	34.9
9	0.2	5	8 : 1	C	72	91 : 9	10.1	22.4
10	0.1	5	16 : 1	C	77	91 : 9	10.1	22.4

[a] Method A: Benzylamine was added in one portion, then the reaction mixture was stirred for 24 h. Method B: The amine was added by a syringe pump over 5 h followed by stirring for 19 h. Method C: The amine was added by a syringe pump over 24 h followed by stirring for 24 h.
[b] The reaction was performed in the presence of 1.0 equiv. of the major product (**PA-1**).

Table 3. Substrate selective condensation with DMT-MM under the improved conditions

Carboxylic acids							Amide		
SA	SB	Amine	HP-β-CD	Method[a]	Solvent ratio $Et_2O : H_2O$	NaCl (M)	Yield[b] (%)	Ratio (**PA** : **PB**)	Relative rate
			none	A	1 : 1	0	53	79 : 21	1.0
			1	B	4 : 1	5	85	99 : 1	26.3
			none	A	1 : 1	0	93	50 : 50	1.0
			0.5	C	8 : 1	5	71	88 : 12	7.3
			none	A	1 : 1	0	100	60 : 40	1.0
			0.5	C	8 : 1	5	89	95 : 5	12.7
			none	A	1 : 1	0	68	56 : 44	1.0
			0.5	C	8 : 1	5	86	95 : 5	14.9
			none	A	1 : 1	0	83	26 : 74	1.0
			0.5	C	8 : 1	5	92	76 : 24	9.0

[a] For Methods A−C, see the footnote to Table 2. [b] Yields were determined by HPLC.



CD	Yield	ratio PA-1	PB-1	PB-2	PB-3
0	56%	23	52	14	11
0.2	82%	87	9	0	4

Figure 1. Selective amidation of a carboxylic acid with the highest affinity for HP-β-CD from the equimolar mixture of four kinds of organic acids (**SA-1**, and **SB-1**, **2**, and **3**)

homogeneous conditions. For this purpose, both the sites are typically connected with each other within a single molecule so that the substrate is brought into close proximity with the reaction site.[1] In our system one would expect the reaction to be inefficient because the reaction site and the starting substrate site are perfectly separated as immiscible phases. By contrast, when a host compound acting as a phase-transfer catalyst is added, substrate specificity is achieved by carrying only the specific guest molecule to the phase in which the activation reagent exists. In this case, the reaction site and substrate binding site do not have to be connected to each other; they need simply to exist in the same phase.

Conclusion

This work has demonstrated that substrate specificity similar to that obtained with a complex artificial enzyme can be achieved by using DMT-MM and a CD, both of which are simple and easily available, as reaction site and substrate binding site, respectively. Although acylations of amines with activated carboxylic acid derivatives under IPTC conditions have been reported previously,[14] to the best of our knowledge, this is the first example of a dehydrocondensation involving a step of carboxylic acid activation under IPTC conditions. We expect this concept to be applicable to various solvent systems composed of fluorous solvents or ionic liquids, and such applications are now under investigation.

Experimental Section

General Remarks: DMT-MM was prepared from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine according to the method reported previously.[6] CDMT was prepared from 2,4,6-trichloro-1,3,5-triazine.[15] All other solvents and chemicals were obtained from commercial sources and used as received unless otherwise noted. Chemical shifts of ^1H- (400 MHz) and ^{13}C NMR

spectra were recorded in ppm (δ) downfield from TMS, which was used as an internal standard.

General Procedure. Method A: An aqueous solution (1 mL) of DMT-MM (0.28 mmol, 1.0 equiv.) was added to a mixture of HP-β-CD (0.28 mmol, 1.0 equiv.), NaCl (0.584 g), 4-*tert*-butylbenzoic acid (**SA-1**; 0.28 mmol, 1.0 equiv.), 3,5-dimethylbenzoic acid (**SB-1**; 0.28 mmol, 1.0 equiv.), and benzylamine (0.56 mmol, 2.0 equiv.) dissolved in a diethyl ether (2 mL)/water (1 mL) biphasic system at room temperature. After being stirred for 24 h at room temperature, the reaction mixture was extracted with diethyl ether and washed successively with saturated sodium carbonate, water, 1 M HCl, water, and brine. The organic layer was dried with $MgSO_4$ and concentrated. The crude product was analyzed by HPLC (Nacalai Tesque COSMOSIL 5C18-AR-II (4.6 × 150 mm), water/MeOH, 65:35, 1.0 mL/min, UV 280 nm) to determine both the yield and the selectivity (yield 80%, **PA-1/PB-1** = 78:22).

Method B: An aqueous solution (0.75 mL) of DMT-MM (0.28 mmol, 1.0 equiv.) was added to a mixture of HP-β-CD (0.28 mmol, 1.0 equiv.), NaCl (0.584 g), 4-*tert*-butylbenzoic acid (**SA-1**; 0.28 mmol, 1.0 equiv.), and 3,5-dimethylbenzoic acid (**SB-1**; 0.28 mmol, 1.0 equiv.) dissolved in a diethyl ether (8 mL)/water (1 mL) biphasic system at room temperature. An aqueous solution (0.25 mL) of benzylamine (0.56 mmol, 2.0 equiv.) was added by a syringe pump over five hours followed by stirring for 19 h at room temperature. The reaction mixture was worked up in the same manner as described in Method A.

Method C: An aqueous solution (0.41 mL) of DMT-MM (0.28 mmol, 1.0 equiv.) was added to a mixture of HP-β-CD (0.28 mmol, 1.0 equiv.), NaCl (0.292 g), 4-*tert*-butylbenzoic acid (**SA-1**; 0.28 mmol, 1.0 equiv.), and 3,5-dimethylbenzoic acid (**SB-1**; 0.28 mmol, 1.0 equiv.) dissolved in a diethyl ether (8 mL)/water (0.35 mL) biphasic system at room temperature. An aqueous solution (0.24 mL) of benzylamine (0.56 mmol, 2.0 equiv.) was added by a syringe pump over 24 h followed by stirring for 24 h at room temperature. The reaction mixture was worked up in the same manner as described in Method A.

***N*-Benzyl-4-*tert*-butylbenzamide:**[5] Colorless crystals; m.p. 143−144 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 3299, 3962, 1635, 1610, 1550 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.32 (s, 9 H), 4.65 (d, J = 5.7 Hz, 2 H), 6.34 (br. s, 1 H), 7.27−7.35 (m, 5 H), 7.42−7.45 (m, 2 H), 7.70−7.74 (m, 2 H) ppm. ESI-MS: m/z = 268 $[M + 1]^+$.

***N*-Benzyl-3,5-dimethylbenzamide:**[5] Colorless crystals; m.p. 107−108 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 3282, 1636, 1600, 1535 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.34 (s, 6 H), 4.63 (d, J = 5.7 Hz, 2 H), 6.33 (br. s, 1 H), 7.12 (s, 1 H), 7.27−7.36 (m, 5 H), 7.38 (s, 2 H) ppm. ESI-MS: m/z = 240 $[M + 1]^+$.

***N*-Benzyl-3,5-di-*tert*-butylbenzamide:**[5] Colorless crystals; m.p. 203−205 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 3241, 2961, 1635, 1594, 1549 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.33 (s, 18 H), 4.67 (d, J = 5.8 Hz, 2 H), 6.36 (br. s, 1 H), 7.27−7.39 (m, 5 H), 7.56 (t, J = 1.8 Hz, 1 H), 7.60 (d, J = 1.8 Hz, 2 H) ppm. ESI-MS: m/z = 324 $[M + 1]^+$.

***N*-Benzyl-2-naphthamide:**[16] Colorless crystals; m.p. 203−205 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 3291, 1637, 1625, 1547, 1415, 1321 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.72 (d, J = 5.6 Hz, 2 H), 6.53 (br. s, 1 H), 7.30−7.43 (m, 5 H), 7.52−7.59 (m, 2 H), 7.84−7.92 (m, 4 H), 8.31 (s, 1 H) ppm. $C_{18}H_{15}NO$ (261.3): calcd. C 82.73, H 5.79; found C 82.66, H 5.86.

***N*-Butyl-4-*tert*-butylbenzamide:** Colorless needles; m.p. 43 °C. IR (KBr): $\tilde{\nu}$ = 3319, 2690, 2932, 2870, 1636, 1611, 1550 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.95 (t, J = 7.3 Hz, 3 H), 1.33 (s, 9 H), 1.36−1.46 (m, 2 H), 1.56−1.63 (m, 2 H), 3.45 (td, J = 7.1, 5.8 Hz, 2 H), 6.08 (br. s, 1 H), 7.42−7.45 (m, 2 H), 7.68−7.71 (m, 2 H) ppm. $C_{15}H_{23}NO$ (233.4): calcd. C 77.21, H 9.93; found C 77.03, H 9.72.

***N*-Butyl-3,5-dimethylbenzamide:** Colorless needles; m.p. 55−56 °C. IR (KBr): $\tilde{\nu}$ = 3308, 2961, 2931, 2871, 1631, 1599, 1536 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.96 (t, J = 7.3 Hz, 3 H), 1.37−1.46 (m, 2 H), 1.56−1.65 (m, 2 H), 2.34 (s, 6 H), 3.44 (td, J = 7.2, 5.8 Hz, 2 H), 6.08 (br. s, 1 H), 7.11 (s, 1 H), 7.35 (s, 2 H) ppm. $C_{13}H_{19}NO$ (205.3): calcd. C 76.06, H 9.33; found C 75.92, H 9.16.

***N*-Benzyl-3-methylbenzamide:** Colorless crystals; m.p. 83−84 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 3309, 1642, 1583, 1551 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.39 (s, 3 H), 4.65 (d, J = 5.7 Hz, 2 H), 6.36 (br. s, 1 H), 7.29−7.37 (m, 7 H), 7.55−7.58 (m, 1 H), 7.62 (s, 1 H) ppm. $C_{15}H_{15}NO$ (225.3): calcd. C 79.97, H 6.71; found C 79.98, H 6.83.

***N*-Benzyloctanamide:** Colorless crystals; m.p. 66 °C (CH_2Cl_2/hexane). IR (KBr): $\tilde{\nu}$ = 3292, 2954, 2929, 2916, 2851, 1633, 1554, 1453, 1431 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.25−1.35 (m, 8 H), 1.62−1.70 (m, 2 H), 2.21 (t, J = 7.6 Hz, 2 H), 4.45 (d, J = 5.7 Hz, 2 H), 5.67 (br. s, 1 H), 7.27−7.36 (m, 5 H) ppm. $C_{15}H_{23}NO$ (233.4): calcd. C 77.21, H 9.93; found C 77.17, H 9.75.

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[1] R. Breslow, S. D. Dong, *Chem. Rev.* **1998**, *98*, 1997−2011, and references cited therein.
[2] [2a] J.-M. Lehn, *Angew. Chem.* **1988**, *100*, 91; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89−112. [2b] D. J. Cram, *Angew. Chem.* **1988**, *100*, 1041; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009−1020. [2c] C. J. Pederson, *Angew. Chem.* **1988**, *100*, 1053; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021−1027. [2d] C. D. Gutsche, *Calixarenes Revisited* (Ed.: J. F. Stoddart, FRS); The Royal Society of Chemistry, **1998**.
[3] [3a] J. C. Harrison, M. R. Eftink, *Biopolymers* **1982**, *21*, 1153−1166. [3b] G. Nemethy, H. A. Scheraga, *J. Chem. Phys.* **1962**, *36*, 3401−3417.
[4] M. Kunishima, C. Kawachi, K. Hioki, K. Terao, S. Tani, *Tetrahedron* **2001**, *57*, 1551−1558.
[5] M. Kunishima, K. Yoshimura, H. Morigaki, R. Kawamata, K. Terao, S. Tani, *J. Am. Chem. Soc.* **2001**, *123*, 10760−10761.
[6] M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki, S. Tani, *Tetrahedron* **1999**, *55*, 13159−13170.
[7] [7a] L. J. Mathias, R. A. Vaidya, *J. Am. Chem. Soc.* **1986**, *108*, 1093−1094. [7b] M. Baur, M. Frank, J. Schatz, F. Schildbach, *Tetrahedron* **2001**, *57*, 6985−6991. [7c] S. Shimizu, K. Kito, Y. Sasaki, C. Hirai, *Chem. Commun.* **1997**, 1629−1630. [7d] S. Shimizu, S. Shirakawa, T. Suzuki, Y. Sasaki, *Tetrahedron* **2001**, *57* 6169−6173. [7e] E. Monflier, S. Tilloy, G. Fremy, Y. Castanet, A. Mortreux, *Tetrahedron Lett.* **1995**, *36*, 9481−9484.
[8] Very recently, a similar concept has been developed by E. Monflie et al. to perform substrate-selective reactions in aqueous organometallic catalysis, see: J. Cabou, H. Bricout, F. Hapiot, E. Monflier, *Catal. Commun.* **2004**, *5*, 265−270.
[9] It seems difficult to explain the observed solvent effect. However, the poor result observed in $CHCl_3$ may be related to the high solubility of Me-β-CD in $CHCl_3$ (> 50 g in 100 mL

$CHCl_3$) (Table 1, Run 4); DMT-MM can be transferred to the organic phase by Me-β-CD.
[10] β-CD was not examined because it could not be dissolved completely under the conditions we employed because of its low solubility in water (maximum concentration is 1.8%).
[11] The dissociation constant determined by UV titration was 6.5×10^{-2} mM.
[12] A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770−790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 707−724.
[13] Similarly, hydrophobic amides were found to precipitate rather than form an inclusion complex with a CD in the CD-based artificial enzyme system.[5]
[14] M. Barra, R. H. de Rossi, *Can. J. Chem.* **1991**, *69*, 1124−1130.
[15] J. S. Cronin, F. O. Ginah, A. R. Murray, J. D. Copp, *Synth. Commun.* **1996**, *26*, 3491−3494.
[16] A. B. Charette, P. Chua, *J. Org. Chem.* **1998**, *63*, 908−909.

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