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PAPER

Cyclopeptoids: a novel class of phase-transfer catalysts†

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The synthesis, complexation properties and catalytic activities under phase-transfer (PT) conditions of differently substituted cyclohexapeptoids are reported. Association constants, for small cationic alkali, and catalytic performances, in a model nucleophilic substitution, are comparable to those of representative crown ethers. Noteworthy, the *N*-[2-(2-methoxyethoxy)ethyl] side chain derivative presents a catalytic efficiency comparable to that of crypt-222, and higher than some commonly used quaternary ammonium salts and crown ethers. Moreover its association constant for Na^+ complexation proved to be higher when compared with dicyclohexyl-18-crown-6. The synthesized cyclohexapeptoids represent the first example of these peptidomimetics in PT catalysis, anticipating interesting applications in biphasic PT methodology.

Introduction

Today phase-transfer catalysis (PTC) is recognized as a versatile methodology for organic synthesis in both industry and academia, because of its general application, efficiency, mild and environment-friendly reaction conditions.[1] Moreover continuing efforts towards the design of new, synthetically versatile catalysts, especially in asymmetric synthesis, are currently being made.[2] Peptoids are an archetypal example of peptidomimetics, which have shown unique structural, chemical and physical properties.[3]

Taking inspiration from the natural cyclopeptides, recently, we studied alkali metal ions complexation[4] and cation transport across a phospholipid membrane[5] for *N*-benzyloxyethyl glycine cyclic oligopeptoids of various sizes, reporting the first metallopeptoid X-ray structure to be solved.[4] The complex association constants, K_a, for the alkali metal ion–host complexes were determined by picrate extraction techniques in H_2O–$CHCl_3$, as described by Cram and co-workers.[6] In particular, the hexacyclo peptoid **1** (Fig. 1) showed a good degree of selectivity for the smaller cations, with a peak for Na^+.[4]

Despite the wide use of peptides and synthetic analogues in catalysis,[7] to the best of our knowledge, to date, peptoid oligomers of *N*-substituted glycines have been scarcely explored for catalytic applications and only one example has been reported in the literature.[8] In this context, the easy access to highly diverse peptoids side chains and backbones, the high-yield solid-phase synthesis, and their well-known metal ion affinities prompted us to investigate the use of cyclopeptoids in the field of PTC.

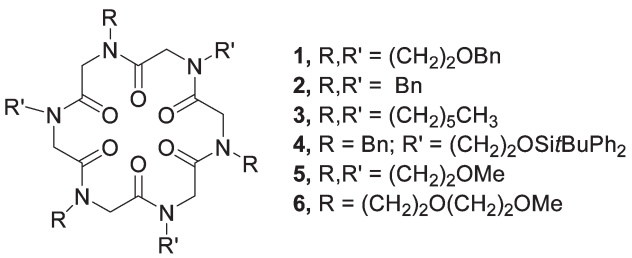

Fig. 1 Structures of the cyclopeptoids examined in our studies.

In this contribution we report the syntheses, binding affinities and catalytic abilities of cyclohexapeptoids **2**–**6** (Fig. 1) in a biphasic nucleophilic substitution reaction and in comparison with well known phase-transfer catalysts.

Results and discussion

Design and synthesis of the new catalysts

The design of an efficient phase transfer catalyst can be a very difficult task since a number of factors are simultaneously involved, often counteracting each other in determining the reaction rate in a two-phase system. Although these factors depend on the experimental conditions and on the kind of reaction, some of them are of general importance for the catalytic efficiency. The lipophilicity of the catalyst, the extraction selectivity, the cation–anion separation within an ion pair and the solvation of the anion must be carefully evaluated to obtain the best results.[9] Similarly to crown ethers, cyclopeptoids are neutral ligands, lacking unwanted, potentially competitive, extraneous anions in

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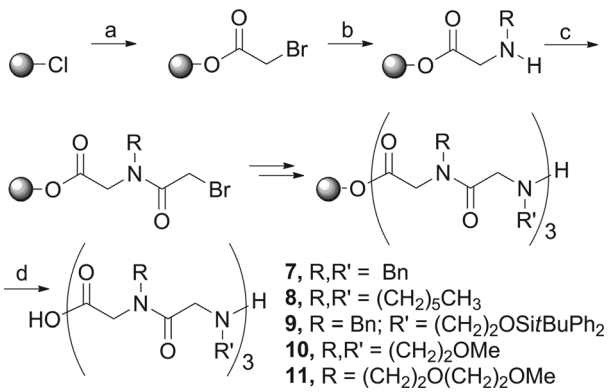
the reaction medium. On the other hand this fact entails uncertainty about the nature of the actual catalyst formed from the ligand–cation complex.

In order to assess the potential of cyclopeptoids as PT catalysts, a series of structurally different cyclohexapeptoids, differing in the nature of the *N*-alkyl side chain, have been prepared taking advantage of the efficient sub-monomer synthetic method.[10] Side chains were designed to guarantee optimal lipophilicity (benzyl and *n*-hexyl appendages) or cation affinity (methoxyethyl and methoxyethoxyethyl pendant groups). The elaboration of the linear precursors, performed on a 2-chlorotrityl resin through a two step construction of the *N*-alkyl glycine, is shown in Scheme 1.

The acylation reaction, using the bromoacetic acid, was followed by a displacement step using the appropriate primary amine. After the completion of synthesis the oligomers were cleaved from the resin using a 1 : 4 solution of hexafluoroisopropanol (HFIP)–CH_2Cl_2. Head-to-tail macrocyclizations of the linear *N*-substituted oligoglycines **7–11** proceeded smoothly giving, under high dilution conditions (3.0×10^{-3} M) and in the presence of the efficient coupling agent *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), the cyclic peptoids **2–6**.[11]

In order to evaluate the use of preformed complexes in the phase-transfer reactions, it was decided to prepare the sodium hexafluorophosphate adducts **12** and **13** shown in Fig. 2 (from neutral **2** and **5**, respectively).



Scheme 1 Sub-monomer approach for the synthesis of oligomers **7–11**. DIPEA = *N*,*N* diisopropylethylamine; DIC = *N*,*N*′-diisopropyl carbodiimide; (a) bromoacetic acid, DIPEA; (b) RNH_2 (10 equiv.); (c) bromoacetic acid, DIC; (d) HFIP–CH_2Cl_2 (1 : 4).

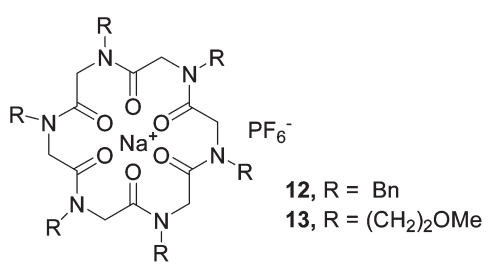


Fig. 2 Complexed cyclopeptoids.

Determination of association constants by Cram's method

Efficient metal complexation is an important requirement for PT catalysts. Table 1 reports the association constants (K_a), as well as $-\Delta G°$ and R_{CHCl_3} values, that have been determined for the complexation of **2–6** to Li^+, Na^+ and K^+ (in H_2O–$CHCl_3$, following Cram's method),[6] in comparison with the dicyclohexyl-18-crown-6 and 15-crown-5 (**14** and **16**, Fig. 3), excellent complexing agents[6,12] and very efficient PT catalysts.[13] While the 18-crown-6 derivatives are known to show high affinity for potassium, 15-crown-5 has been found to be selective for sodium.[7,14]

Table 1 Parameters for association between hosts and picrate salts in $CHCl_3$ at 25 °C

Entry	Complexing agent	M^+	R_{CHCl3}[a]	$K_a \times 10^{-4}/M^{-1}$	$-\Delta G°$/kcal mol^{-1}
1	2[b]	Li^+	0.13	63	7.9
2		Na^+	0.22	120	8.3
3	3	Li^+	0.24	170	8.5
4		Na^+	0.32	260	8.8
5		K^+	0.12	31	7.5
6	5	Li^+	0.07	27	7.4
7		Na^+	0.32	250	8.7
8		K^+	0.03	5.1	6.4
9	6	Li^+	0.38	490	9.1
10		Na^+	0.55	1500	9.8
11		K^+	0.48	590	9.2
12	14[c]	Li^+	0.053	19.2	7.20
13		Na^+	0.308	234	8.68
14		K^+	0.809	20 000	11.32
15	16	Li^+	<0.01	<3	—
16		Na^+	0.49	884	9.5
17		K^+	0.10	23	7.3

[a] [Guest]/[Host] in $CHCl_3$ layer at equilibrium obtained by direct measurement, or calculated by difference from measurement made on aqueous phase. [b] For compound **2** it was not possible to determine the association constant with the potassium picrate for the formation of a precipitate (probably an insoluble complex with the salt). [c] See ref. 6.

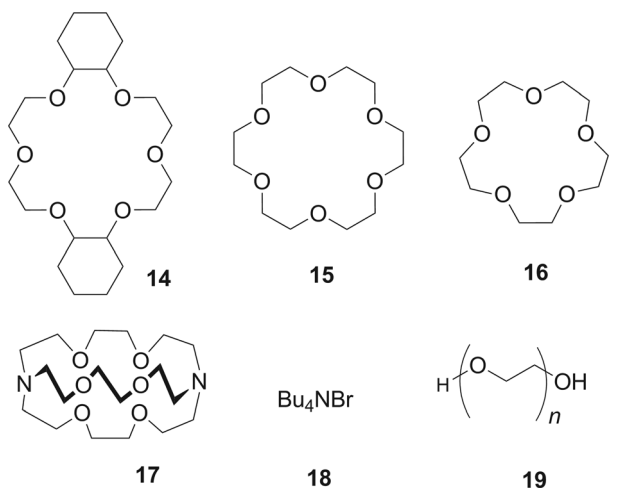


Fig. 3 Crown ethers and other complexing agents discussed in this article.

The synthesized cyclopeptoids exhibited a good degree of selectivity towards Na^+, as previously observed for **1**[4] (**6** being the most efficient). In particular, the macrocycle **6** showed a K_a value for Na^+ higher than that determined for 15-crown-5 (**16**) and more than six times greater than that calculated for dicyclohexyl-18-crown-6 (**14**).

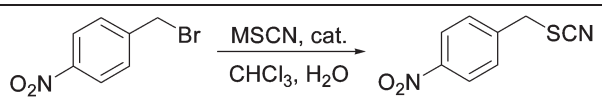
Catalytic activities and comparison with other phase transfer catalysts

In order to assess the ability of the cyclopeptoids as PT catalysts, the substitution reaction of *p*-nitrobenzyl bromide, in a liquid–liquid two phase system, using sodium or potassium thiocyanate, was chosen. These phase-transfer reactions were found to obey pseudo-first order kinetics. Moreover, the observed rates of the reaction were proportional to the amount of the catalyst and the process was found to take place in the organic layer.[13,15]

All reactions were carried out in a $CHCl_3$–H_2O two-phase system, with 5 mol% of catalyst loading. The reactions were monitored chromatographically in order to evaluate the time required for total conversion. All the reactions were stopped within 24 hours and the percentage of conversion was measured by ^{1}H-NMR. Table 2 depicts the activities of the synthesized cyclohexapeptoids compared to some commonly used commercially available PT catalysts, namely dicyclohexyl-18-crown-6 (**14**), 18-crown-6 (**15**), 15-crown-5 (**16**), crypt-222 (**17**), tetrabutylammonium bromide (**18**), poly(ethylene glycol) (average M_n 300, **19**) (Fig. 3).

As can be seen from the comparison with the uncatalyzed reaction (entry 1), all the new compounds (**2–6** and **12–13**, entries 2–8) catalyzed the substitution reaction.

Table 2 S_N2 reaction with NaSCN and KSCN catalyzed by cyclopeptoids and common PT catalysts[a]



		NaSCN		KSCN	
Entry	Catalyst	Time (h)	Conversion (%)	Time (h)	Conversion (%)
1	—	24	10	24	5
2	**2**	24	95	13	>99
3	**3**	4.5	>99	24	53
4	**4**	12	>99	24	71
5	**5**	8	>99	24	91
6	**6**	2.5	>99	7.5	>99
7	**12**	24	55	24	79
8	**13**	24	78	24	30
9	**14**	6.5	>99	3	>99
10	**15**	24	>99	7.5	>99
11	**16**	8	>99	1	>99
12	**17**	2	>99	1	>99
13	**18**	4.5	>99	4.5	>99
14	**19**	24	81	24	85

[a] All the reactions were carried out using a 0.25 M solution of *p*-nitrobenzyl bromide in $CHCl_3$ (0.4 mL, 0.10 mmol), a 0.75 M aqueous solution of NaSCN or KSCN (0.2 mL, 0.15 mmol) and catalyst (0.005 mmol).

It is noteworthy to mention that while all the commercially available PT catalysts (**14–19**) were more efficient in the presence of potassium thiocyanate, with almost all the new cyclohexapeptoids the reaction proved to be faster with sodium thiocyanate. An exception was cyclopeptoid **2**, both in the free and complexed form (entries 2 and 7, respectively). Interestingly, the catalysts in the complexed form (**12** and **13**, entries 7 and 8) were shown to be less efficient than those in the free form (**2** and **5**). All the uncomplexed cyclopeptoids proved to be more effective catalysts than the known poly(ethylene glycol) **19**. The most active cyclopeptoids, **3**, **5** and **6**, exhibited activities comparable with the crown ethers. To our delight, macrocycle **6**, containing *N*-[2-(2-methoxyethoxy)ethyl] side chains, showed, in the reaction with NaSCN, higher efficiency than crown ethers, and an activity comparable to that observed for cryptand **17**, the best one among the screened catalysts. A high activity, albeit lower, was achieved also with KSCN as the reagent.

As previously pointed out, the design of an efficient catalyst and the rationalization of the experimental results are intrinsically difficult tasks. Anyhow, some general considerations can be drawn from the observed experimental data. The poor performance of the complexed catalysts **12** and **13** could be attributed to the low solubility of such compounds in the reaction solvent. This observation also comes from the comparison of reactions carried out with the macrocycles **2–6**. The better solubility for the compounds **3–6** relative to the products **2**, **12** and **13**, achieved with the introduction of a more lipophilic *N*-alkyl chain, led to reduced reaction times. The solubility in chloroform is not the only parameter to be taken into account. The very soluble compound **4**, indeed, proved to be less active than **3**, **5** and **6**, probably due to the presence of the bulky silyl group. More complex is the interpretation of the data obtained for the *N*-benzyl glycine hexacyclopeptoid both in free and complexed form (**2** and **12**) which showed an opposite trend to that of the other macrocycles. In fact, shorter reaction times and a higher conversion were observed using potassium thiocyanate. Unfortunately, for the macrocycle **2** it was not possible to determine the K_a for K^+, in order to compare it with those estimated for the other ions. However, K_a values for Na^+ were found to be lower than that of the other macrocycles, which might explain the poorer activity of this catalyst. Indeed, the data determined by Cram's method support the results observed in catalysis since compound **6**, which shows the greatest K_a values, proved to be the best catalyst.

Conclusions

In conclusion, this paper highlights the potential of the cyclopeptoids as phase transfer catalysts, proving their applicability in the case of the nucleophilic substitution reaction of *p*-nitrobenzyl bromide with thiocyanate salts, in a two-phase liquid–liquid system. Notably, the macrocycle **6** containing *N*-[2-(2-methoxyethoxy)ethyl] side chains showed K_a values for Na^+ greater than that reported for the efficient complexing agents dicyclohexyl-18-crown-6 (**14**) and 15-crown-5 (**16**). Moreover, **6** exhibited high catalytic activity in the reaction with NaSCN, comparable to that evaluated for cryptand **17** and higher than those displayed by commonly used crown ethers and the tetrabutylammonium

bromide. Good activity was also achieved in the reaction with KSCN.

The present contribution represents the first example of the use of cyclopeptoids in PTC. Considering the enormous potential of peptoids in the exploration of chemical space, we firmly believe in further developments of these systems in liquid–solid two-phase reactions, and especially in the asymmetric phase-transfer catalysis. Studies in this regard are currently in progress.

Experimental

General information

Reactions involving air or moisture sensitive reagents were carried out under nitrogen atmosphere using freshly distilled solvents. Toluene and dichloromethane were distilled from calcium hydride under nitrogen. Glassware was flame-dried (0.05 Torr) prior to use. When necessary, compounds were dried *in vacuo* over P_2O_5, by azeotropic removal of water with toluene under reduced pressure. Starting materials and reagents purchased from commercial suppliers were generally used without purification. Reactions were monitored by TLC on silica gel plates (0.25 mm) and visualized by UV light or by spraying with ninhydrin solutions and drying with iodine. Flash chromatography was performed on Silica Gel 60 (particle size: 0.040–0.063 mm) and the solvents employed were of analytical grade. HPLC analysis was performed on C_{18} reversed-phase analytical and semipreparative columns (Waters, Bondapak, 10 μm, 125 Å, 3.9 mm × 300 mm and 7.8 × 300 mm, respectively) using a Modular HPLC System JASCO LC-NET II/ADC equipped with a JASCO Model PU-2089 Plus Pump and a JASCO MD-2010 Plus UV-vis multiple wavelength detector set at 220 nm.

Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure materials. The NMR spectra were recorded on a Bruker DRX 400 (^{1}H at 400.13 MHz, ^{13}C at 100.03 MHz). Chemical shifts (δ) are reported in ppm relative to the residual solvent peak ($CHCl_3$, δ = 7.26; $^{13}CDCl_3$, δ = 77.0; CD_2HCN: δ = 1.94; $^{13}CD_3CN$: δ = 1.39) and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintuplet; m, multiplet; bs, broad singlet. Coupling constants (J) are quoted in hertz. High resolution ESI-MS spectra were performed on a Q-Star Applied Biosystem mass spectrometer. ESI-MS analysis in positive ion mode was performed using a Finnigan LCQ Deca ion trap mass spectrometer (ThermoFinnigan, San Josè, CA, USA) and the mass spectra were acquired and processed using the Xcalibur software provided by Thermo Finnigan.

General procedure for sub-monomer solid-phase synthesis of the linear peptoids 7–11[11]

Linear peptoid oligomers **7–11** were synthesized using a sub-monomer solid-phase approach. In a typical synthesis 2-chlorotrityl chloride resin (2,α-dichlorobenzhydryl-polystyrene cross-linked with 1% DVB; 100–200 mesh; 1.3 mmol g^{-1}, 0.60 g, 0.78 mmol) was swelled in dry CH_2Cl_2 (6 mL) for 45 min and washed twice with dry DMF (6 mL). The first sub-monomer was attached onto the resin by adding bromoacetic acid (173 mg, 1.25 mmol) in dry CH_2Cl_2 (3 mL) and DIPEA (680 μL, 3.9 mmol) on a shaker platform for 60 min at room temperature, followed by washing with dry CH_2Cl_2 (6 mL) and then with DMF (3 × 6 mL). To the bromoacetylated resin was added a DMF solution of the desired amine (1 M, 6 mL). All the amines are commercially available except for the methoxyethoxymethyl amine, which was prepared through a rapid two step sequence, as described in the literature.[16] The mixture was left on a shaker platform for 30 min at room temperature, then the resin was washed with DMF (3 × 3 mL). Subsequent bromoacetylation reactions were accomplished by reacting the aminated oligomer with a solution of bromoacetic acid (1.08 g, 7.80 mmol) in DMF (6 mL) and of DIC (1.3 mL, 8.40 mmol) for 40 min at room temperature. The filtered resin was washed with DMF (3 × 6 mL) and treated again with the amine under the same conditions reported above. This cycle of reactions was iterated until the target oligomer was obtained. The cleavage was performed by treating twice the resin, previously washed with CH_2Cl_2 (3 × 6 mL), with a solution of HFIP in CH_2Cl_2 (20% v/v, 8 mL) on a shaker platform at room temperature for 30 min and 5 min, respectively. The resin was then filtered away and the combined filtrates were concentrated *in vacuo*. The final products were dissolved in 50% acetonitrile in HPLC grade water and analyzed by RP-HPLC [purity >95% for oligomers **7–9**, 65% for oligomers **10–11**; conditions: 5 → 100% B in 30 min for oligomers **7–10**, 25 → 100% B in 50 min for oligomer **11** (A, 0.1% TFA in water, B, 0.1% TFA in acetonitrile); flow: 1 mL min^{-1}, 220 nm]. The linear oligomers were subjected to the cyclization reaction without further purification with the exception of **11** which was purified by semipreparative RP-HPLC [conditions: 25%–100% B in 50 min (A, 0.1% TFA in water, B, 0.1% TFA in acetonitrile); flow: 2 mL min^{-1}, 220 nm].

8: 61% (crude residue); ES-MS: 865.9 m/z $[M + H]^+$; t_R: 20.3 min;

9: 76% (crude residue); ES-MS: 1477.7 m/z $[M + H]^+$; t_R: 26.4 min;

10: 65% (crude residue); ES-MS: 709.1 m/z $[M + H]^+$; t_R: 10.4 min;

11: 69% (purified by RP-HPLC); ES-MS: 973.5 m/z $[M + H]^+$; t_R: 7.8 min.

General procedure for the cyclization reactions: synthesis of compounds 2–6[11]

A solution of the linear peptoids (**7–11**) (0.36 mmol), previously co-evaporated three times with toluene, was prepared under nitrogen in dry DMF (12 mL). The mixture was added dropwise by a syringe pump in 2 h to a stirred solution of HATU (548 mg, 1.44 mmol) and DIPEA (389 μL, 2.23 mmol) in dry DMF (110 mL) at room temperature in anhydrous atmosphere. After 12 h the resulting mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 (80 mL) and a solution of HCl (0.5 M, 40 mL). The mixture was extracted with CH_2Cl_2 (2 × 80 mL) and the combined organic phases were washed with water (120 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The cyclic products were dissolved in 50% acetonitrile in HPLC grade water and analyzed by RP-HPLC [purity >95% for oligomers **2–6**, conditions: 5%–100% B in 30 min for cycles **2–5**, 25%–100% B in 50 min for cycle **6** (A, 0.1% TFA in water, B,

0.1% TFA in acetonitrile); flow: 1 mL min^{-1}, 220 nm]. The crude residues **2**, **3** and **5** were purified by precipitation in acetonitrile–water 1 : 1 and **5** and **6** by RP-HPLC on a C_{18} reversed-phase semi-preparative column, t_R: 18.0 min and t_R: 15.4 min, respectively, conditions: 5%–100% B in 30 min for compound **5**, 25%–100% B in 50 min for compound **6** [(A, 0.1% TFA in water, B, 0.1% TFA in acetonitrile); flow: 2 mL min^{-1}, 220 nm].

3: 37%; white amorphous solid; HR-ESI MS: *m/z* 869.6809 $[M + Na]^+$(calcd for $C_{48}H_{90}N_6NaO_6^+$ 869.6814); ES-MS: 869.7 *m/z* $[M + Na]^+$, t_R: 23.2 min; ^{1}H-NMR: (400 MHz, $CDCl_3$, mixture of rotamers) δ: 4.73–3.76 (m, 12 H, $COCH_2N$), 3.58–2.70 (m, 12 H, $NCH_2(CH_2)_4CH_3$), 2.05–1.20 (m, 48 H, $NCH_2(CH_2)_4CH_3$), 0.89–0.83 (bs, 18 H, $NCH_2(CH_2)_4CH_3$); ^{13}C-NMR: (100 MHz, $CDCl_3$, mixture of rotamers) δ: 171. 8 (bs), 171.5 (bs), 171.0 (bs), 170.5 (bs), 170.3 (bs), 170.2 (bs), 169.9 (bs), 169.5 (bs), 169.2 (bs), 169.1 (bs), 168.8 (bs), 168.6 (bs), 168.4 (bs), 168.3 (bs), 168.2 (bs), 168.0 (bs), 167.6 (bs), 167.4 (bs), 167.3 (bs), 166.8 (bs), 166.7 (bs), 166.4 (bs), 166.3 (bs), 51.5 (bs), 51.1 (bs), 50.9 (bs), 50.4 (bs), 50.0 (bs), 49.7 (bs), 49.5 (bs), 49.3 (bs), 49.0 (bs), 48.8 (bs), 48.7 (bs), 48.6 (bs), 48.3 (bs), 48.2 (bs), 47.9 (bs), 47.7 (bs), 47.5 (bs), 47.3 (bs), 47.1 (bs), 46.8 (bs), 46.6 (bs), 46.3 (bs), 46.0 (bs), 43.3 (bs), 32.7 (bs), 31.6 (bs), 31.5 (bs), 30.1 (bs), 30.0 (bs), 29.9 (bs), 29.7 (bs), 29.4 (bs), 29.1 (bs), 29.0 (bs), 28.9 (bs), 28.7 (bs), 28.5 (bs), 28.1 (bs), 28.0 (bs), 27.7 (bs), 27.6 (bs), 27.5 (bs), 27.3 (bs), 27.2 (bs), 27.0 (bs), 26.9 (bs), 26.5 (bs), 22.6 (s), 14.0 (s).

4: 51%; white amorphous solid; HR-ESI MS: *m/z* 1481.6911 $[M + Na]^+$ (calcd for $C_{87}H_{102}N_6NaO_9Si_3^+$ 1481.6908); ES-MS 1481.7 *m/z* $[M + Na^+]$; t_R: 28.2 min; ^{1}H-NMR: (400 MHz, $CDCl_3$, mixture of rotamers) δ: 7.68–6.89 (m, 45 H, Ar), 5.36–5.24, 4.75–2.71 (m, 30 H, $COCH_2N$, NCH_2CH_2O–, NCH_2CH_2O), 1.25–0.82 (m, 27 H, $SiC(CH_3)_3$; ^{13}C-NMR: (100 MHz, $CDCl_3$, mixture of rotamers) δ: 171. 8 (bs), 171.3 (bs), 170.4 (bs), 170.2 (bs), 170.1 (bs), 169.7 (bs), 169.5 (bs), 169.1 (bs), 168.9 (bs), 168.6 (bs), 168.1 (bs), 167.8 (bs), 167.7 (bs), 167.6 (bs), 167.2 (bs), 167.0 (bs), 137.1 (bs), 136.7 (bs), 135.4 (bs), 134.7 (bs), 133.5 (bs), 133.0 (bs), 132.8 (bs), 129.9 (bs), 129.8 (bs), 129.6 (bs), 129.0 (bs), 128.6 (bs), 128.3 (bs), 127.9 (bs), 127.7 (bs), 127.2 (bs), 126.9 (bs), 126.8 (bs), 125.3 (bs), 82.8–79.7 (bs), 63.3 (bs), 62.9 (bs), 62.6 (bs), 62.3 (bs), 62.0 (bs), 61.7 (bs), 61.3 (bs), 61.0 (bs), 60.6 (bs), 53.2 (bs), 52.6 (bs), 51.8 (bs), 51.5 (bs), 51.1 (bs), 50.8 (bs), 50.5 (bs), 50.0 (bs), 49.7 (bs), 49.1 (bs), 48.3 (bs), 48.1 (bs), 47.7 (bs), 47.4 (bs), 47.0 (bs), 46.6 (bs), 46.2 (bs), 32.0 (bs), 31.6 (bs), 31.4 (bs), 31.2 (bs), 30.9 (bs), 30.6 (bs), 29.7 (bs), 26.9 (bs).

5: 29%, by HPLC; white amorphous solid; HR-ESI MS: *m/z* 691.3869 $[M + H]^+$ (calcd for $C_{30}H_{55}N_6O_{12}^+$ 691.3872); ES-MS: 691.8 *m/z* $[M + H^+]$, 713.7 *m/z* $[M + Na^+]$; t_R: 11.8 min; ^{1}H-NMR: (400 MHz, $CDCl_3$, mixture of rotamers) δ: 10.1 (CF_3COOH), 4.92–3.86 (m, 12 H, $COCH_2N$), 3.86–2.80 (m, 42 H, NCH_2CH_2O–, NCH_2CH_2O, OCH_3 overlapped); ^{13}C-NMR: (100 MHz, $CDCl_3$, mixture of rotamers) δ: 171. 5 (bs), 171.0 (bs), 170.6 (bs), 170.1 (bs), 170.0 (bs), 169.8 (bs), 169.7 (bs), 169.5 (bs), 169.3 (bs), 169.1 (bs), 168.9 (bs), 168.7 (bs), 168.2 (bs), 168.1 (bs), 158.7 (q, J = 40 Hz, CF_3COOH), 115.0 (q, J = 285 Hz, CF_3COOH), 71.7 (bs), 71.5 (bs), 71.4 (bs), 71.3 (bs), 71.0 (bs), 70.8 (bs), 70.6 (bs), 70.2 (bs), 70.0 (bs), 69.8 (bs), 69.6 (bs), 69.3 (bs), 69.1 (bs), 68.8 (bs), 68.7 (bs), 59.1 (bs), 58.9 (bs), 58.6 (bs), 58.2 (bs), 53.4 (bs), 52.5 (bs), 52.3 (bs), 50.9 (bs), 50.7 (bs), 50.4 (bs), 50.3 (bs), 50.2 (bs), 49.9 (bs), 49.1 (bs), 48.7 (bs), 48.4 (bs), 48.3 (bs), 48.0 (bs), 47.6 (bs), 47.4 (bs), 47.0 (bs), 46.8 (bs), 46.6 (bs), 45.9 (bs), 45.5 (bs), 43.3 (bs).

6: 42%, by HPLC; yellow oil; HR-ESI MS: *m/z* 955.5449 $[M + H]^+$ (calcd for $C_{42}H_{79}N_6O_{18}^+$ 955.5455); ES-MS 955.5 *m/z* $[M + H^+]$; t_R: 10.6 min; ^{1}H-NMR: (400 MHz, $CDCl_3$, mixture of rotamers) δ: 4.94–3.32 (m, 42 H, $COCH_2N$, OCH_2CH_2O–, OCH_2CH_2O, NCH_2CH_2O–, NCH_2CH_2O, OCH_3 overlapped); ^{13}C-NMR: (100 MHz, $CDCl_3$, mixture of rotamers) δ: 172.6, 172.3, 171.3, 170.9, 170.7, 170.5, 170.1, 169.7, 169.4, 169.0, 168.9, 168.4, 168.3, 168.0, 71.8, 71.8, 70.4, 70.3, 70.2, 70.1, 69.8, 69.7, 69.4, 69.2, 69.0, 68.8, 68.7, 68.5, 68.0, 67.8, 67.4, 58.9, 52.4, 51.0, 50.3, 49.5, 49.3, 48.8, 48.1, 47.3, 46.3.

General procedure for the synthesis of complexed cyclopeptoids 12 and 13

To a solution of cyclopeptoid **2** or **5** (0.034 mmol) in CH_2Cl_2 : MeOH (9 : 1) sodium hexafluorophosphate (5.6 mg, 0.034 mmol) was added. The mixture was stirred overnight and then concentrated *in vacuo*.

12: quant.; white amorphous solid; ES-MS: 883.9 *m/z* $[M + H^+]$, 905.4 $[M + Na^+]$; ^{1}H-NMR: (400 MHz, CD_3CN) δ: 7.37–7.26 (m, 30 H, Ar), 4.86 (d, 6 H, J = 16.8 Hz, CH*H*Ar), 4.72 (d, 6 H, J = 16.3 Hz, NC*H*HCO), 4.41 (d, 6 H, J = 16.8 Hz, C*H*HAr), 3.72 (d, J = 16.3 Hz, 6 H, NCH*H*CO); ^{13}C-NMR: (100 MHz, CD_3CN) δ: 171.7, 136.8, 129.8 (×3), 128.9, 128.7, 53.2, 50.8.

13: quant.; white amorphous solid; ES-MS 713.7 *m/z* $[M + Na^+]$; ^{1}H-NMR: (400 MHz, CD_3CN) δ: 4.69 (d, 6 H, J = 16.7 Hz, NC*H*HCO), 3.84 (d, 6 H, J = 16.7 Hz, NCH*H*CO), 3.59–3.33 (m, 24 H, NCH_2CH_2O and NCH_2CH_2O), 3.34 (s, 18 H, OCH_3); ^{13}C-NMR: (100 MHz, CD_3CN) δ: 170.6, 71.0, 59.1, 50.5, 49.6.

Determination of binding affinities for compounds 2, 3, 5, 6 and 16

Association constants K_a were calculated from the equation $K_a = K_e/K_d$, according to methodology reported by Cram and coworkers.[6] K_d values, which represent the distribution constants of the picrate salts between water and $CHCl_3$, were previously determined by Cram,[6] while K_e values were calculated following the "ultraviolet method" reported by Cram and coworkers.[6] All ultraviolet (UV) measurements were made on a Varian Cary 50 UV-Vis Spectrophotometer at 380 nm at 24–26 °C, using spectrophotometric grade solvents. The picrate salts were prepared according to literature procedures,[17] and dried under high vacuum before use. Aqueous solutions were prepared that were 0.0150 M in the picrate of Li^+, Na^+, K^+. Aliquots of these solutions (250 μL of Li^+, Na^+, K^+) were introduced in six Eppendorf vials, and to each of these, 250 μL of a 0.015 M solution of the host in $CHCl_3$ was added. The vials were capped (in order to prevent evaporation) and mixed thoroughly, using a Vortex "Maxi Mixer", for 5 minutes and then centrifuged (1000 rpm). Aliquots of 50 μL of each aqueous phase were diluted with

CH_3CN up to 5.0 mL. Successively 200 μL of these solutions were diluted with CH_3CN up to 1.0 mL. Aliquots of 100 μL of each organic phase were also diluted with CH_3CN up to 5.0 mL. Successively 200 μL of the latter solutions were diluted with CH_3CN up to 1.0 mL. The absorbance of each sample was then measured against the appropriate blank solution at 372 nm at 25 °C. R, K_e, K_a and $\Delta G°$ were thus calculated in the proper way.[6]

General procedure for the substitution reaction using 2–6, 13, 14 and commercially available PTC catalysts 14–19

To a solution of *p*-nitrobenzyl bromide (21.5 mg, 0.10 mmol) in $CHCl_3$ (0.25 M, 0.200 mL), containing 5 mol% of the catalyst, a 0.75 M aqueous solution of thiocyanate salt (0.15 mmol) was added and the resulting mixture was stirred for up to 24 hours in total. The reaction was monitored by TLC at intervals of 30 minutes. The mixture was filtered through a short-path silica gel column and removal of the solvent *in vacuo* afforded a residue that was analyzed by ^{1}H-NMR to determine the % of conversion.

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