Efficient chirality transcription utilizing a cerium(IV) double decker porphyrin: a prototype for development of a molecular memory system

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A cerium(IV) double decker porphyrin **2** bearing two pairs of 4-pyridyl groups and two pairs of 3,5-dimethoxyphenyl groups was synthesized. In the presence of chiral dicarboxylic acid guests with a two carbon spacer [*e.g.*, (1*R*,2*R*)-cyclohexane-1,2-dicarboxylic acid and Boc-L-aspartic acid] **2** gave a CD-active species. The plots of the CD intensity *vs.* the guest concentration showed a sigmoidal curvature, a sign of homotropic, positive allosterism. Analysis according to the Hill equation indicated that the guests were bound autoacceleratively. Even after the chiral guests were removed by the addition of excess pyridine, **2** remained CD-active because of its inherent chirality. Thereafter, the CD intensity decreased very slowly as a result of internal rotation of the porphyrin subunits. Thermodynamic analysis of this racemization process gave $\Delta G^{\ddagger}_{298} = 23.0$ kcal mol^{-1}, $\Delta H^{\ddagger}_{298} = 18.1$ kcal mol^{-1} and $\Delta S^{\ddagger}_{298} = -16.4$ cal mol^{-1} K^{-1}. Observations and calculations indicate that the chiral memory can be preserved for 3 days at 0 °C and for one year at −37 °C. In conclusion, this is a rare artificial system for which a homotropic, positive allosterism is observable and in which the guest chirality is transcribed and stored.

Introduction

Positive and negative allosteric effects are seen throughout nature where biological events must be efficiently regulated in response to chemical or physical signals from the outside world. Typical examples include cooperative dioxygen binding to hemoglobin,[1] hexamerization of the arginine repressor[2] and a cooperative effect with respect to the concentration of arachidonate-containing phospholipids in cytosolic phospholipase A_2,[3] among others.[4] The biomimetic design of such allosteric systems is of great significance in order to efficiently regulate the complexation ability or the catalytic activity of artificial receptors according to an allosteric manner.[5–14] Furthermore, this methodology is very useful to amplify and convert weak chemical or physical signals into other signals which are convenient for us to read out and record.

We have previously designed a porphyrin-based cerium(IV) bis(porphyrinate) double decker **1** which shows a unique positive, homotropic allosterism.[15] In this system, the binding event of the first dicarboxylic acid guest to a pair of pyridyl groups can suppress the rotation of the two porphyrin planes without inducing a plane inclination;†[16] the subsequent binding of the three dicarboxylic acid guests to the remaining three pairs of pyridyl groups can then occur autoacceleratively.[15] The use of chiral dicarboxylic acid guests that could induce a chiral orientation of two porphyrins is a logical progression for this theme with the added feature of obtaining chiral transcription,[17] if the orientation can be preserved, through positive allosterism. With this object in mind we designed compound **2**:[18] that is, we used only two pairs of guest-binding pyridyl groups to simplify the system and two pairs of bulky 3,5-dimethoxyphenyl groups to suppress the porphyrin plane rotation. It was found that the chiral twist in the two porphyrin planes in **2** could be formed in an enantiomeric excess by the binding of two chiral dicarboxylic acid guests and that this chirality can be stored for several hours even at room temperature (Scheme 1).

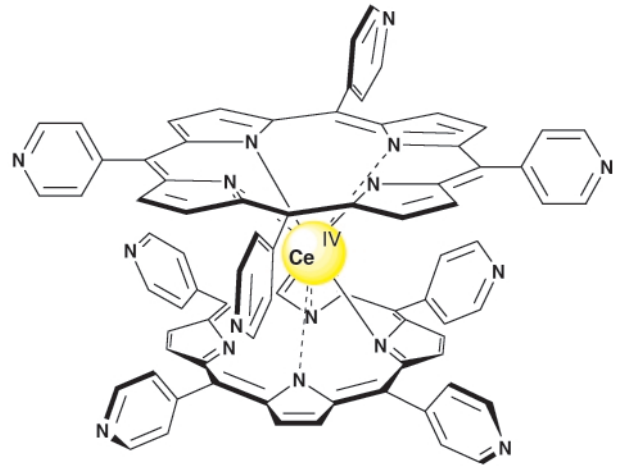
† It is known that the rate of the porphyrin ring rotation in Ce·bis(porphyrinate) double deckers is comparable with or slower than the NMR timescale. However, allosteric behavior is observable for the present system as long as the porphyrin rings are able to rotate, albeit slowly: see refs. 16 and 17.

Results and discussion

Synthesis and variable temperature ^{1}H NMR spectra

Compound **2** was synthesized from 3,5-dimethoxybenzaldehyde, pyridine-4-aldehyde and pyrrole according to Scheme 2 and identified by ^{1}H NMR (COSY at −40 °C: the peaks were broadened at room temperature) and MALDI-TOF-MS (*m*/*z* 1609) spectral evidence and elemental analysis.

^{1}H NMR spectroscopy (600 MHz) at −40 °C in CD_2Cl_2, revealed two pairs of doublets for the pyridyl protons (δ_H 6.46 and 8.55 ppm for the *exo* protons and δ_H 9.39 and 9.46 ppm for the *endo* protons) and two singlets for the methoxy protons (δ_H 3.56 and 4.46 ppm). The peak split implies that the rotational speed of these aromatic substituents is slower than the NMR timescale[19] at this temperature. With a rise in temperature (solvent: CD_2Cl_2 at −40–30 °C and $Cl_2CDCDCl_2$ at 60–110 °C) the peaks for the pyridyl protons and the methoxy protons were gradually broadened and finally coalesced at 30 °C and 110 °C, respectively which indicates that the rotation of the bulky 3,5-dimethoxyphenyl groups is much slower than that of the 4-pyridyl groups. The pyrrole protons appeared as two pairs of doublets (at −40 °C, δ_H 8.16 and 8.35 ppm and 8.39 and 8.62 ppm), indicating that, as expected from the stereochemistry of the double-decker porphyrin system, the distal pyrroles are equivalent whereas the proximal pyrroles are inequivalent. In contrast to the temperature dependence of the aromatic substituents, these pyrrole peaks were scarcely affected by the temperature change at −40–110 °C implying that the speed of the porphyrin ring rotation is much slower than the ^{1}H NMR timescale.[19] Judging from previous examples,[15–17] however, rotation of the porphyrin rings still occurs, albeit on a significantly slow timescale; this behavior is discussed further below.



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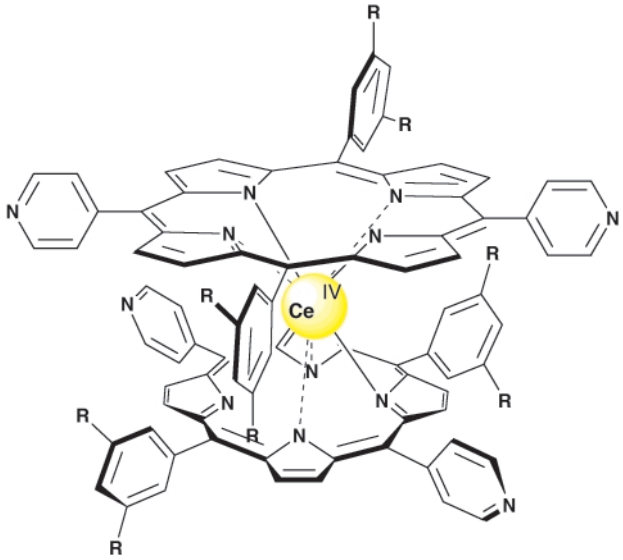


2

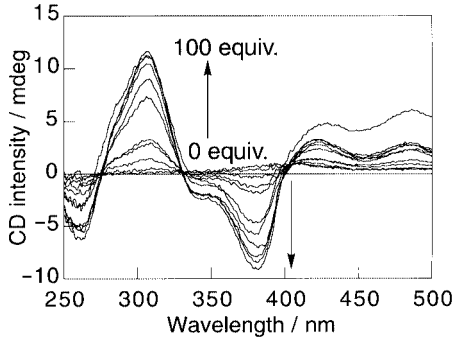


Fig. 1 Concentration dependence of the CD spectra: [**2**] = 1.00×10^{-4} mol dm^{-3}, [**3**] = 0–15×10^{-3} mol dm^{-3}, CH_2Cl_2–ethyl acetate = 30 : 1 v/v, 25 °C. The **2** + **4** system also showed a similar spectral change.

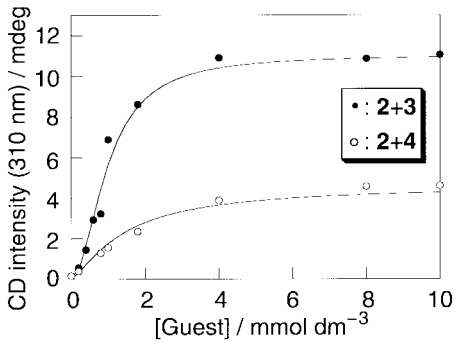


Fig. 2 Plots of CD intensity at 310 nm *vs.* [**3**] or [**4**].

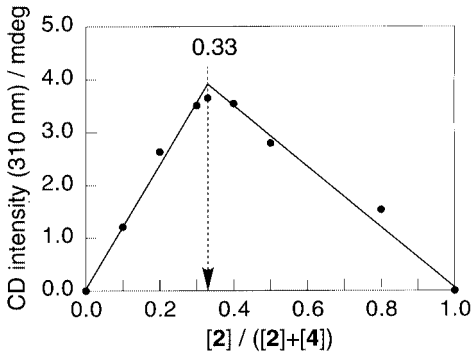
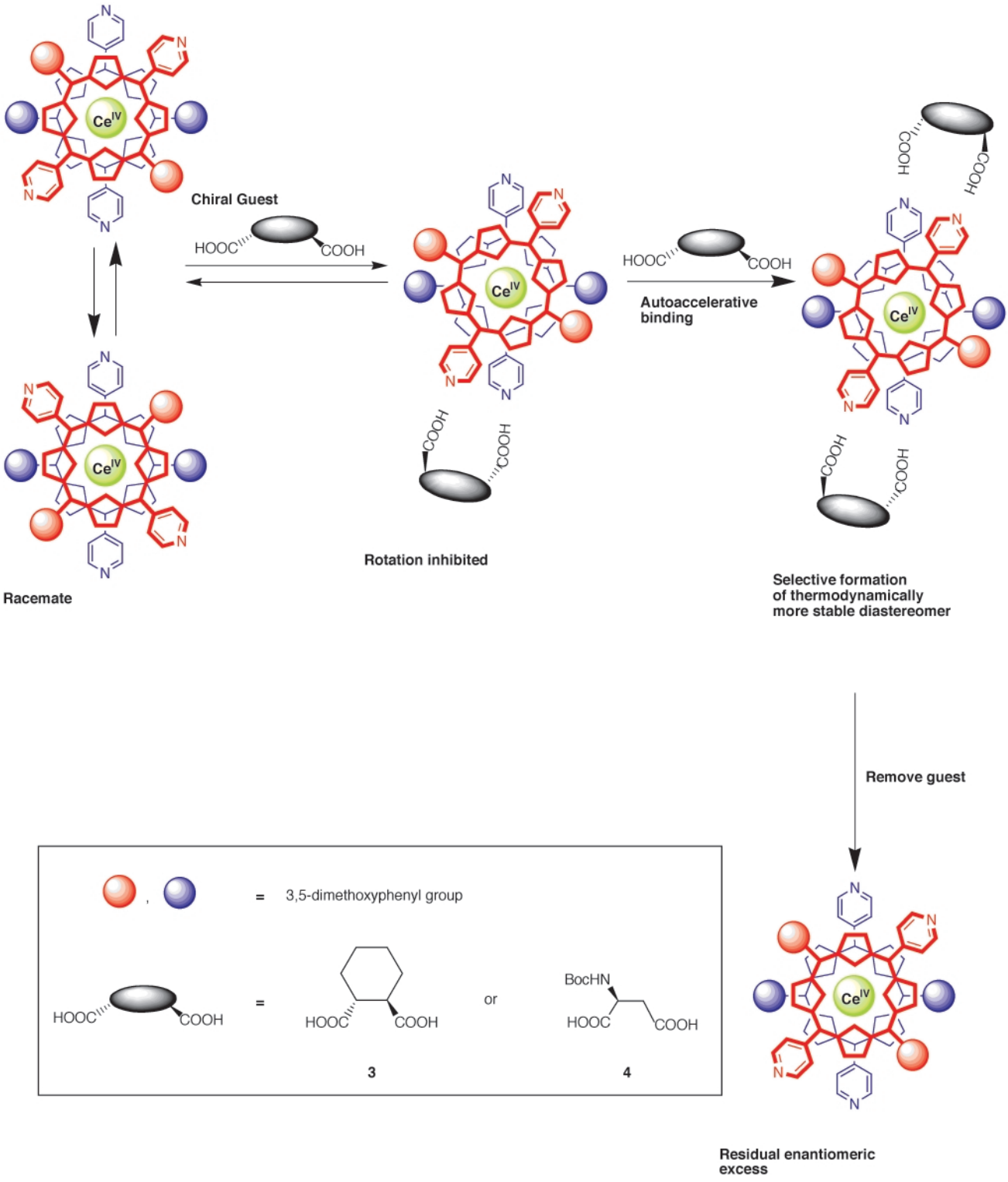


Fig. 3 Job plot: the [**2**] + [**4**] value is maintained as a constant (1.00×10^{-3} mol dm^{-3}), CH_2Cl_2–ethyl acetate = 30 : 1 v/v, 25 °C.

Homotropic, positive allosterism observable for the CD-active species

The symmetry of **2** is such that it can exist as a pair of enantiomeric rotamers that can interconvert slowly to produce a racemate. When chiral dicarboxylic acids with a two-carbon spacer such as (1*R*,2*R*)-cyclohexane-1,2-dicarboxylic acid (**3**) and Boc-L-aspartic acid (**4**) were added, a CD-active species appeared gradually and the CD spectra reached an equilibrium after 3 h at 25 °C (Figs. 1 and 2). Importantly, the plots of CD intensities *vs.* guest concentration at equilibrium featured a sigmoidal curvature which is a sign of homotropic, positive allosterism.[13,15] This cooperative guest-binding process can be analyzed according to the Hill equation:[20] $\log(y/(1-y)) = n \log[\text{guest}] + \log K$, where K and n are the association constant and Hill coefficient, respectively and $y = K/([\text{guest}]^{-n} + K)$. From the slope and the intercept of the linear plots we obtained $K = 8.51 \times 10^5$ (mol $dm^{-3})^{-2}$ and $n = 1.97$ for **3** (correlation coefficient 0.96) and $K = 5.62 \times 10^3$ (mol $dm^{-3})^{-2}$ and $n = 1.32$ for **4** (correlation coefficient 0.97). Since the K value for **3** is larger by 151-fold than that for **4** and the n value is closer to 2.0, one can consider that **3** exerts a sharper positive allosterism. In the previous system using **1**, the K value for **3** [2.75×10^9 (mol $dm^{-3})^{-4}$] was smaller than that for **4** [2.63×10^{11} (mol $dm^{-3})^{-4}$]. This difference indicates that the guest selectivity is sensitively influenced by substituent effects. Judging from the X-ray crystallographic analysis of double decker porphyrins, the planes are warped toward the exohedral direction in order to reduce electrostatic and/or steric repulsion.[21] Compound **1** can be classified into this type. On the other hand, when bulky substituents are introduced into the *meso*-aryl groups of porphyrins, they tend to adopt a saddle conformation due to the steric repulsion.[17,22] Compound **2** is classified, more or less, into this type. Flexible guest **4** can cope with this conformational change whereas rigid guest **3** cannot. This difference should appear as guest selectivity between **1** and **2**. The 1 : 2 stoichiometry of the CD-active complexes was further corroborated by a Job plot.[23] As shown in Fig. 3, a plot of the CD intensity at 310 nm against [**2**]/([**2**] + [**4**]) results in a maximum at 0.33 which supports the view that the complex consists of one host **2** and two guests **4**.

The foregoing findings indicate that the binding of the first dicarboxylic acid guest suppresses the rotational freedom of the two porphyrin planes, which facilitates the binding of the second dicarboxylic acid guest. As a result, two pairs of pyridyl groups in **2** cooperatively bind these chiral guest molecules and the two porphyrin planes are immobilized asymmetrically to yield the CD-active species. This is a rare artificial system for which a homotropic, positive allosterism with $n = 2$ is observable. It is undoubted that the present allosterism emerges from a



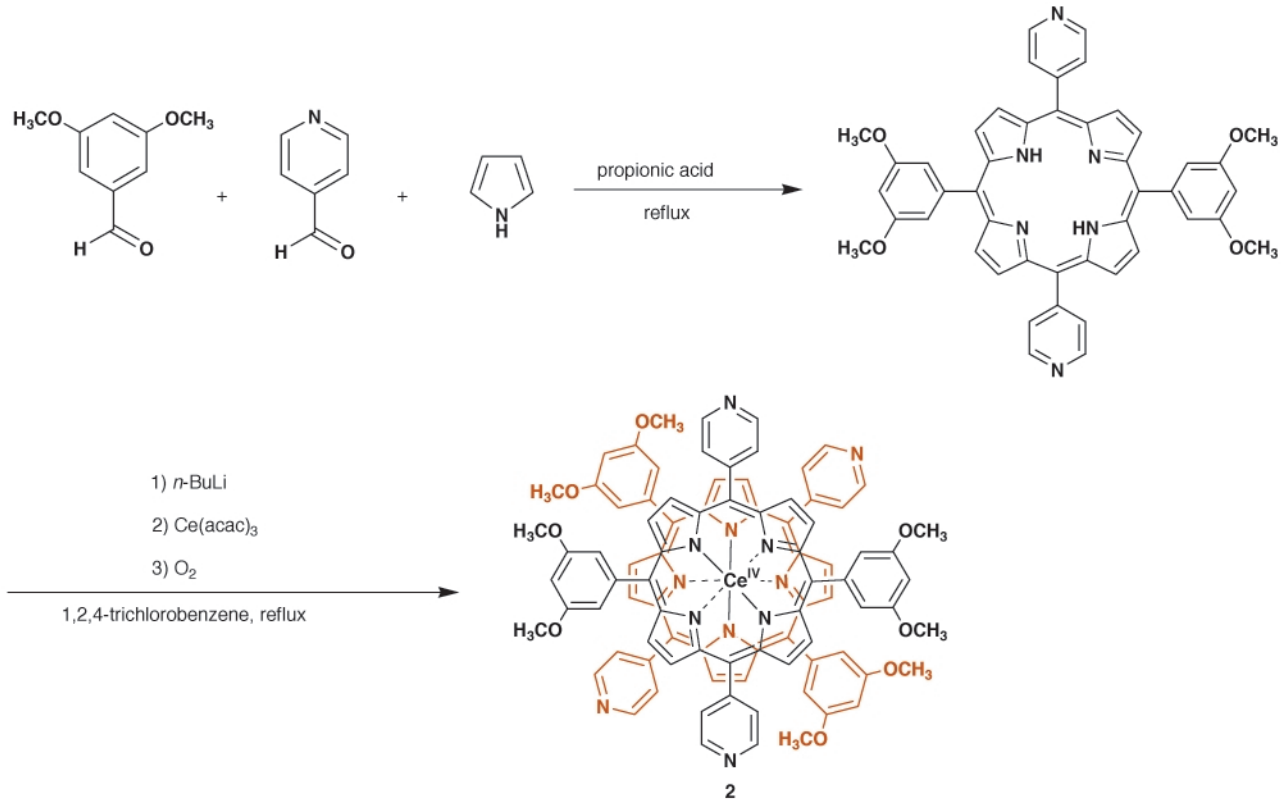
Scheme 1

unique situation where the first guest, binding to the pyridine-based receptor site suffers an entropic penalty in suppressing the porphyrin ring rotation whereas the second guest-binding to the now preorganized pyridine receptor site does not incur this same penalty.

Dynamic aspects of chiral memory preservation

In contrast to the conspicuous CD spectral changes, the UV–VIS absorption spectra were scarcely changed by addition of **3** or **4**. As shown in Fig. 4, the λ_{max} of the Soret band (398 nm) shifted by only 1 nm to a longer wavelength in the presence of **3**. When excess pyridine (0.40 mol dm^{-3}) was added, the Soret band immediately shifted to 398 nm which is coincident with that in the absence of **3**. In ^{1}H NMR spectroscopy, the pyridine protons (δ_H 6.41 and 9.37 ppm) shifted to a lower field region (δ_H 6.61 and 9.60 ppm) in the presence of **3** (Fig. 5). When excess pyridine-d_5 (0.40 mol dm^{-3}) was added, the peaks moved to the original chemical shifts observed in the absence of **3**. These results consistently support the view that the **2**·**3**·**3** complex is immediately dissociated by the addition of excess pyridine.

When excess pyridine was added to a CD-active solution containing **2** and **3**, the CD spectral shape immediately changed as



Scheme 2

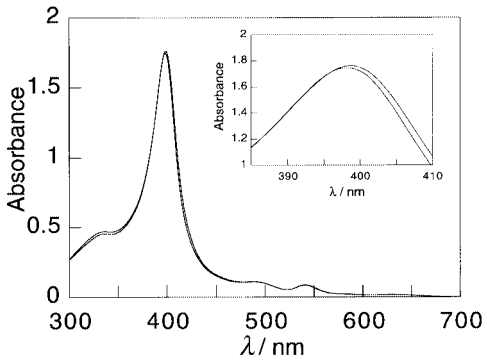


Fig. 4 Absorption spectra of **2** (1.00×10^{-4} mol dm^{-3}) in the absence and the presence of **3** (1.00×10^{-2} mol dm^{-3}): 0.1 cm cell, CH_2Cl_2–ethyl acetate = 30 : 1 v/v, 25 °C.

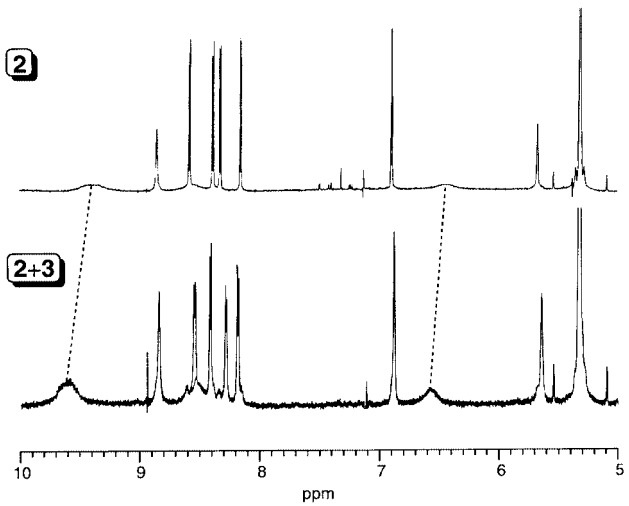


Fig. 5 ^{1}H NMR spectra (600 MHz) of **2** (1.00×10^{-4} mol dm^{-3}) in the absence and the presence of **3** (1.00×10^{-2} mol dm^{-3}): CD_2Cl_2–$CD_3COOC_2D_5$ = 30 : 1 v/v, 25 °C.

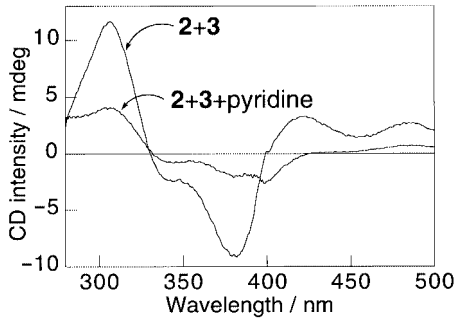


Fig. 6 CD spectral change induced by the addition of excess pyridine (25 °C): [**2**] = 1.00×10^{-4} mol dm^{-3}, [**3**] = 1.00×10^{-2} mol dm^{-3}, [pyridine] = 4.00×10^{-1} mol dm^{-3}, CH_2Cl_2–ethyl acetate = 30 : 1 v/v.

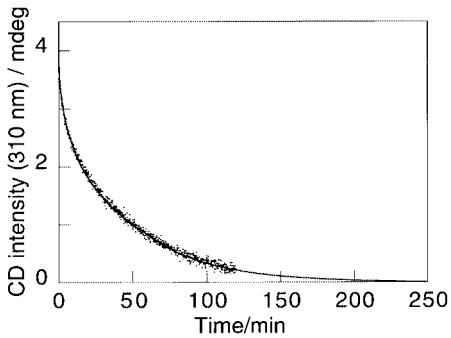


Fig. 7 Time dependence of the CD intensity at 310 nm which reflects the inherent chirality of **2**, CH_2Cl_2–ethyl acetate = 30 : 1 v/v, 25 °C.

illustrated in Fig. 6. Since the **2**·**3**·**3** complex has been dissociated by this treatment, the new CD spectrum can be assigned to the inherent chirality of **2**; *i.e.*, either the right-handed or the left-handed species exists over the other at this stage. As shown in Fig. 7, the CD intensity gradually decreased and finally reached zero after 3 h which corresponds to racemization caused by the slow porphyrin ring rotation. The time depend-

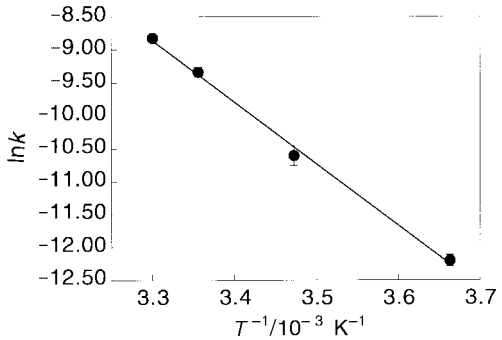


Fig. 8 Arrhenius plot for k_{rac}.

ence satisfied first-order kinetics and the racemization rate constant (k_{rac}) was estimated to be 8.79 (± 0.67) × 10^{-5} s^{-1} at 25 °C. Similar experiments were conducted at 0, 15 and 30 °C and the k_{rac} values were analyzed according to an Arrhenius plot (Fig. 8). From the slope and the intercept of the linear relationship (correlation coefficient 0.996), we obtained E_a = 18.7 kcal mol^{-1}, $A = 3.85 \times 10^9$ s^{-1}, $\Delta G^{\ddagger}_{298}$ = 23.0 kcal mol^{-1}, $\Delta H^{\ddagger}_{298}$ = 18.1 kcal mol^{-1}, $\Delta S^{\ddagger}_{298} = -16.4$ cal mol^{-1} K^{-1}. The thermodynamic parameters thus obtained indicate that at 0 °C the chiral memory is preserved for 3 days (as estimated by the half-life). If it is reasonable to extrapolate this linear relationship to a lower temperature region, this chirality can be estimated to be preserved for one year at −37 °C and 1.9×10^6 years at −100 °C.

Conclusions

We have demonstrated that **2** shows a positive allosteric effect with Hill coefficients of 1.32–1.97; such positive, homotropic effects are very rare in artificial systems.[13,15] In addition, the porphyrin ring rotation speed is suppressed by two bulky 3,5-dimethoxyphenyl groups which has enabled us to preserve a transcribed chiral memory in **2** for a significant life time. We believe that further elaboration of the present system might eventually lead to a novel molecular memory storage system.[24]

Experimental

All starting materials and solvents were purchased from Tokyo Kasei Organic Chemicals or Wako Organic Chemicals and were used as supplied. Silica gel supplied by Merck (Silica gel 60, 230–400 mesh).

Spectra

UV–VIS and CD spectra were obtained with CH_2Cl_2–EtOAc = 30 : 1 (v/v) solutions as solvent in 1 mm quartz cells. UV–VIS spectra were performed using a Shimadzu UV-2500 PC spectrophotometer; CD spectra were performed using a JASCO J-720WI spectrophotometer and ^{1}H NMR spectra obtained using a BrukerDMX 600 spectrometer.

Synthesis

5,15-Bis(3,5-dimethoxyphenyl)-10,20-bis(4-pyridyl)porphyrin and bis[5,15-bis(3,5-dimethoxyphenyl)-10,20-bis(4-pyridyl)porphyrinato]cerium(IV) were synthesised according to the method of Buchler and coworkers.[18]

5,15-Bis(3,5-dimethoxyphenyl)-10,20-bis(4-pyridyl)porphyrin. 3,5-Dimethoxybenzaldehyde (4.0 g, 24 mmol) and pyridine-4-carbaldehyde (3.4 g, 28 mmol) were added to propionic acid (160 ml) and the mixture heated to ~120 °C. Pyrrole (4.1 g, 50.7 mmol) was then added and the mixture heated to reflux for 2.5 h, after which time the solution was cooled and the solvent removed by distillation *in vacuo*. The residue was dissolved in acetone (15 ml) and crude porphyrin precipitated by the addition of *n*-hexane (70 ml). The mixture of porphyrins thus obtained were separated by column chromatography [silica, $CHCl_3$–acetone = 5 : 1 (v/v)] to yield 5,15-bis(3,5-dimethoxyphenyl)-10,20-bis(4-pyridyl)porphyrin as a purple solid (90 mg, 1%). Analysis: δ_H ($CDCl_3$) −2.87 (2H, s), 3.97 (12H, s), 6.91 (2H, s), 7.38 (4H, d, *J* 2), 8.15 (4H, d, *J* 4), 8.78 (4H, d, *J* 4), 9.00 (8H, d, *J* 4); mp >300 °C (decomp.).

Bis[5,15-bis(3,5-dimethoxyphenyl)-10,20-bis(4-pyridyl)porphyrinato]cerium(IV) (2). To a stirred solution of 5,15-bis-(3,5-dimethoxyphenyl)-10,20-bis(4-pyridyl)porphyrin (100 mg, 0.135 mmol) in 1,2,4-trichlorobenzene (60 ml) *n*-butyllithium (3.5 ml of a 1.54 M solution in hexane, 5.4 mmol) was added dropwise at room temperature. The mixture was heated to 200 °C before $Ce(acac)_3 \cdot nH_2O$ (0.59 g, 1.3 mmol) was added. The mixture was then brought to reflux for 4 h before being cooled to room temperature and removal of the solvent by distillation *in vacuo*. The residue was purified by column chromatography [silica, $CHCl_3$–acetone = 20 : 1 (v/v)] to yield **2** as a brown solid (40 mg, 37%). Analysis: δ_H ($CDCl_3$) 3.56 (12H, s), 4.46 (12H, s), 5.52 (4H, d), 6.46 (4H, d), 6.91 (4H, s), 8.16 (4H, d), 8.35 (4H, d), 8.39 (4H, d), 8.55 (4H, d), 8.62 (4H, d), 8.88 (4H, d), 9.39 (4H, d), 9.46 (4H, d); *m*/*z* (HRMS) 1609.4409 (calcd for M + H^+ = 1609.4416), calcd for $C_{92}H_{68}CeN_{12}O_8 \cdot 4H_2O$: C, 65.35%; H, 4.59%; N, 9.94%; found: C; 65.47%, H, 4.50%; N, 9.63%.

Acknowledgements

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