Chiral Amplification

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Amplified Chiral Transformation through Helical Assembly**

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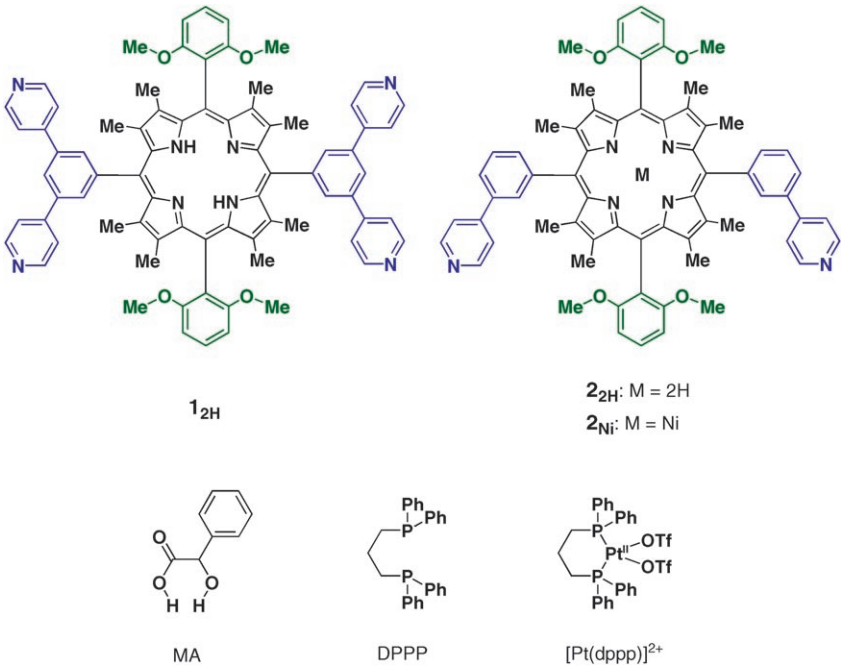
"Chiral amplification" is a phenomenon in which products with a higher enantiomeric purity than those of applied chiral auxiliaries are formed.[1–6] This is one of the challenging subjects in asymmetric synthesis and is also interesting in view of the use of chiral symmetry breaking in nature. Successful examples so far reported include: 1) homo/heterochiral assembly of catalysts themselves or with ligands or 2) the participation of chiral products or intermediates in the formation of transition states of the reaction, resulting in stereoselective acceleration or deceleration of certain elementary steps.[1,2] Herein we report a conceptually new strategy toward "chiral amplification" in asymmetric transformations by prior conversion of a substrate into a helical polymeric precursor. Several covalent polymers, which are capable of dynamic helical inversion, are known to form a one-handed helical conformation when they accommodate chiral auxiliaries covalently or noncovalently.[3–6] Some of them are able to achieve one handedness even when the appended chiral auxiliaries are not enantiomerically pure. This phenomenon has been referred to as the "majority rule", in which a major enantiomer determines the helical handedness.[3] We expected this to be applicable to "chiral amplification" in asymmetric synthesis when appropriate reactions that are mediated by such helical environments are chosen.



For the first step in the realization of this concept, we attempted Pt^{II}-induced supramolecular polymerization[7] of a D_2-symmetric, fully substituted porphyrin ($\mathbf{1_{2H}}$) with four pyridyl groups. Because of a steric repulsion among the neighboring substituents, fully substituted porphyrins adopt a nonplanar, saddle shape and therefore porphyrins such as $\mathbf{1_{2H}}$ with a point group D_2 are chiral.[8] However, owing to a low energetic barrier for the macrocyclic inversion, these nonplanar porphyrins undergo a rapid interconversion between the two enantiomeric forms. In 1997, we reported that such a dynamic chirality of saddle-shaped porphyrins (SP) becomes frozen into either of the two diastereoisomeric forms when they interact with a chiral acid such as (*R*)- or (*S*)-mandelic acid (MA; Scheme 1).[9] Interestingly, although SP loses interacting MA when poured into AcOH, it preserves the absolute configuration, transferred from MA, thanks to the regenerated hydrogen bonds with AcOH (chirality memory).[9–11] More recently, we have also reported that, in a cyclic dimer of SP, the two facing SP units are configurationally interlocked with one another, so that the cyclic dimer

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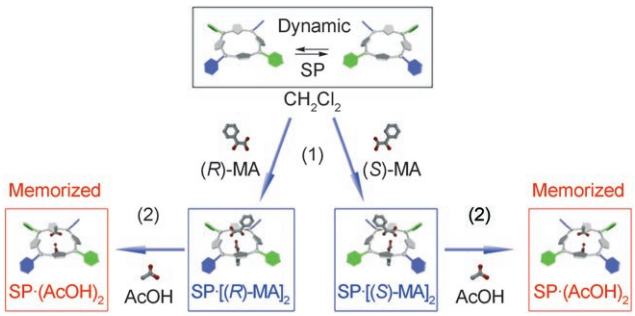
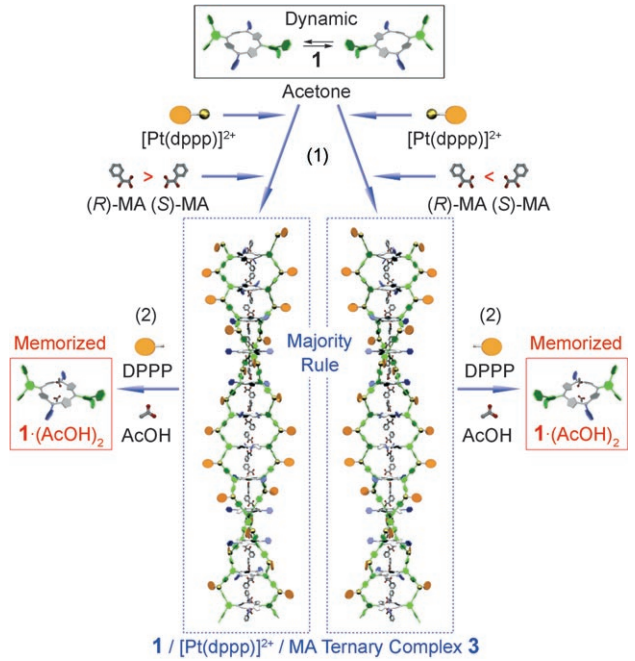


Scheme 1. Schematic representations of 1) chirality transfer from mandelic acid (MA) to a D_2-symmetric saddle-shaped porphyrin (SP) through hydrogen-bonding interactions (SP·MA$_2$) and 2) memorization of the resulting configurations in acetic acid (AcOH) in the form of SP·(AcOH)$_2$.

entirely adopts a helically twisted conformation.[9d] With these features in mind, along with the basic idea of "chiral amplification" (see before), we herein investigated effects of MA on the CD profiles of a polymer, which was possibly formed by Pt^{II}-induced supramolecular polymerization of $\mathbf{1_{2H}}$ (Scheme 2). As the opposed *meso*-aryl groups of $\mathbf{1_{2H}}$ are twisted relative to one another in either a clockwise or a counterclockwise direction,[9] the polymer, if it adopts a ladder shape (**3**), is expected to form a helical conformation. Provided that the "majority rule"[3–6] operates in helical **3**, one handedness might result even when applied MA is not enantiomerically pure. Thus, stereoretentive depolymerization of **3**, by taking advantage of the chirality-memorizing ability of the monomer, could give $\mathbf{1_{2H}}$ with an "amplified enantiomeric purity".

Similar to SP compounds so far reported,[9] pyridine containing $\mathbf{1_{2H}}$, upon interaction with (*R*)- or (*S*)-MA (1:2) in CH_2Cl_2, turned optically active. The CD sign of $\mathbf{1_{2H}}$ with (*R*)-MA was opposite to that of (*S*)-MA (Figure 1b). Furthermore, even when the complex with (*R*)- or (*S*)-MA was poured into AcOH, $\mathbf{1_{2H}}$ remained CD active without any substantial decrease in intensity over 5 h at 20 °C.[9] Thus, $\mathbf{1_{2H}}$ possesses a "chiroptical memory" (Scheme 1). For the Pt^{II}-



Scheme 2. Proposal of chiral amplification of $\mathbf{1_{2H}}$ by the "majority rule" operative in a coordination polymer from $\mathbf{1_{2H}}$ and $[Pt(dppp)]^{2+}$. Schematic representations of the experimental procedures and expected products: 1) $[Pt(dppp)]^{2+}$-induced polymerization of $\mathbf{1_{2H}}$ in acetone followed by the treatment with a mixture of (*R*)- and (*S*)- MA (0–100% *ee*) and 2) dissociation of resultant polymer **3** in DPPP-containing AcOH, affording the diacetate complex of $\mathbf{1_{2H}}$ ($\mathbf{1_{2H}}$·(AcOH)$_2$).

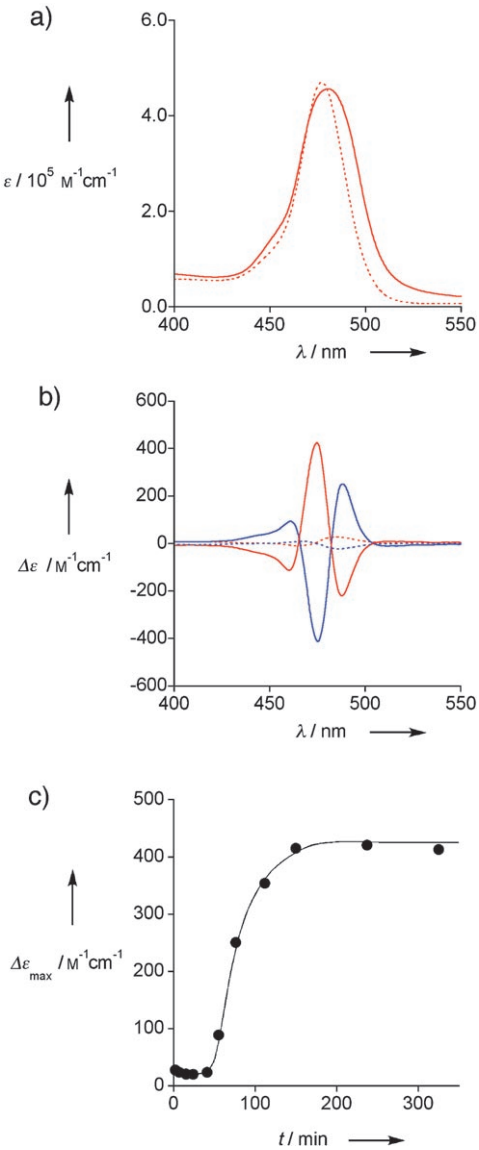
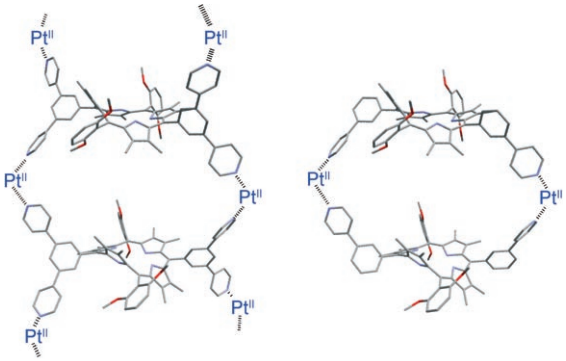


Figure 1. Complexation of $\mathbf{1_{2H}}$ (4 mM) and MA (8 mM) in the presence (——) and absence (-----) of $[Pt(dppp)]^{2+}$ (6 mM) in acetone at 20 °C. a) Absorption and b) CD spectra after 300-fold dilution with CH_2Cl_2. Red and blue curves represent the spectra with (*R*)- and (*S*)-MA, respectively. c) CD spectral intensity ($\Delta\varepsilon_{max}$) change at λ_{max} (474–480 nm) of the ternary mixture of $\mathbf{1_{2H}}$, $[Pt(dppp)]^{2+}$, and (*R*)-MA as a function of the immersion time in acetone. t = immersion time in acetone.

induced supramolecular polymerization (Scheme 2),[7] an acetone solution of $[Pt(dppp)]^{2+}$ (dppp = 1,3-bis(diphenylphosphino)propane; OTf = triflate) was added to that of $\mathbf{1_{2H}}$, and after the mixture was stirred for 40 min, (*R*)-MA was added. The resulting ternary mixture ($c\mathbf{1_{2H}} = 4$ mM, $c[Pt(dppp)]^{2+} = 6$ mM, c(*R*)-MA = 8 mM) was immersed for 12 h at 20 °C and then diluted by 300 fold with CH_2Cl_2 for absorption and CD spectroscopic measurements. Compared with the case without $[Pt(dppp)]^{2+}$ (Figure 1a, -----), the absorption spectrum of $\mathbf{1_{2H}}$ in the ternary mixture was red-shifted by 3 nm and was also much broader (solid curve). In the Soret absorption region of $\mathbf{1_{2H}}$ (Figure 1b), the ternary mixture displayed distinct CD bands (——), which are different in shape and significantly enhanced from that without $[Pt(dppp)]^{2+}$ (-----). As expected, the use of (*S*)-MA instead of (*R*)-MA resulted in a mirror-image CD spectrum (——). Interestingly, although the ternary mixture was immersed in acetone, the CD intensity was enhanced sigmoidally (Figure 1c). After an initial induction period (≈40 min), a marked CD enhancement suddenly took place followed by a plateau, which occurred at 160 min. At this stage, the addition of an opposite enantiomer of MA to the mixture no longer caused CD sign inversion.

The ternary mixture showed a broad ^{1}H NMR spectrum in $CDCl_3$, which is probably due to a slow conformational change of the presumed coordination polymer. Therefore, we synthesized $\mathbf{2_{2H}}$, a reference SP bearing only two pyridyl groups,[12] with an expectation that it could form a metal-bridged cyclic dimer in a manner analogous to that expected



Coordination Polymer of **1** with $[Pt(dppp)]^{2+}$ (Proposed)

Cyclic Dimer of **2** with $[Pt(dppp)]^{2+}$

for the polymerization of $\mathbf{1_{2H}}$ (Scheme 2). To avoid complexity owing to the protonation of $\mathbf{2_{2H}}$, its nickel complex ($\mathbf{2_{Ni}}$) was allowed to coordinate with $[Pt(dppp)]^{2+}$ in $CHCl_3$. As expected, cold-spray ionization mass spectrometry (CSI-MS) [13] of their equimolar mixture displayed intense peaks at $m/z = 1814$, 1160, and 832,[12] which were assigned to the process of the 2:2 complex losing its $CF_3SO_3^-$ counter anions at the ionization step. No peaks assignable to higher oligomers were detected. In $CDCl_3$ at 20 °C, the cyclic dimer showed a triplet ^{31}P NMR signal at δ −14.6 ppm ($J_{P-Pt} = 1532$ Hz) owing to $[Pt(dppp)]^{2+}$ and a singlet ^{19}F NMR signal at δ −78.6 ppm owing to $CF_3SO_3^-$.[12] Because of the coordination to $[Pt(dppp)]^{2+}$, the pyridyl groups of $\mathbf{2_{Ni}}$ showed downfield-shifted ^{1}H NMR signals from those of monomeric $\mathbf{2_{Ni}}$.[12] In contrast, other peripheral groups of the $\mathbf{2_{Ni}}$ units displayed upfield-shifted signals possibly owing to their mutual magnetic shielding. The selective cyclodimerization of $\mathbf{2_{Ni}}$ with $[Pt(dppp)]^{2+}$, thus observed, may support our hypothesis that its tetrapyridyl version ($\mathbf{1_{2H}}$) possibly forms ladder polymer **3** with $[Pt(dppp)]^{2+}$ (Scheme 2).[7]

Interestingly, the chiroptical activity of the ternary mixture of $\mathbf{1_{2H}}$, $[Pt(dppp)]^{2+}$, and MA, when immersed in acetone at 20 °C, showed a nonlinear response to the *ee* value of the applied MA (Figure 2a, ●). For example, the $\Delta\varepsilon_{max}$ value, observed with enantiomerically pure (*R*)-MA, was achieved by using (*R*)-MA with only 40% *ee*. In sharp contrast, the $\mathbf{1_{2H}}$–MA binary mixture without $[Pt(dppp)]^{2+}$ showed a linear increase in $\Delta\varepsilon_{max}$ with the *ee* value of MA (Figure 2a, ○). The ternary complex in CH_2Cl_2 neither displayed time-dependent CD spectral enhancement nor a nonlinear CD response to the enantiomeric purity of MA.[12] We noticed that the immersion of the ternary mixture in acetone (Figure 1c) results in the formation of tiny green particles. Dynamic light scattering (DLS) analysis showed that the particles are 38 nm to 1.9 μm in size with an average radius of 0.2 μm (Figure 3a). According to polarized optical microscopy, the particles are semicrystalline and tabular.[12]

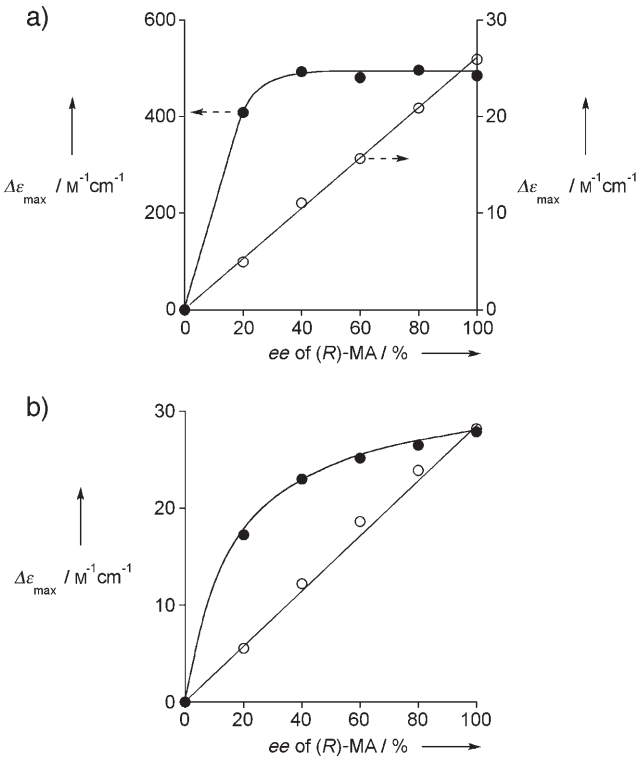


Figure 2. Complexation of $\mathbf{1_{2H}}$ (4 mM) and MA (8 mM, *ee* = 0, 20, 40, 60, 80, and 100% for *R*) in the presence (●) and absence (○) of $[Pt(dppp)]^{2+}$ (6 mM) in acetone at 20 °C. a) $\Delta\varepsilon$ values at λ_{max} of the samples after 300-fold dilution with CH_2Cl_2. b) $\Delta\varepsilon$ values at λ_{max} of the samples after 300-fold dilution with an acetic acid (AcOH) solution of DPPP ([DPPP]/[Pt^{II}] = 25). The samples were immersed for 12 h in acetone prior to the dilution for CD spectroscopy.

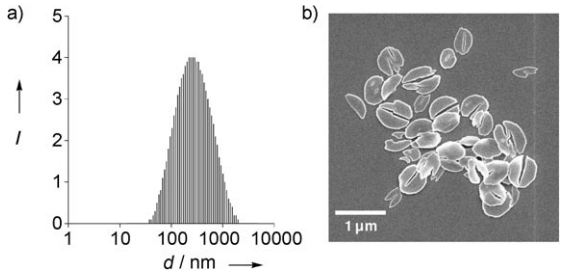


Figure 3. a) DLS analysis showed that the particles have an average radius of 0.2 µm. b) SEM of an air-dried sample of the suspension showed leaf-shaped objects. *d* = diameter.

Scanning electron microscopy (SEM; Figure 3b) of an air-dried sample of the suspension showed leaf-shaped objects approximately 500 nm wide and, judging from their height profile in atomic force microscopy (AFM), 20 nm thick.[12] According to elemental analysis, the leaf-shaped objects, which were isolated by filtration, contained Pt with a N/Pt/P ratio of 8.2:2.0:4.3. The isolated green particles were hardly soluble in $CHCl_3$ but gradually soluble in an $[D_4]$-AcOH solution of DPPP ($[DPPP]/[Pt^{II}] = 25$), affording a homogeneous solution. Here, DPPP presumably breaks the N–Pt^{II}–N linkages in the complex by ripping off the bridging $[Pt(dppp)]^{2+}$ moieties, whereas AcOH kicks out (*R*)-MA from $\mathbf{1_{2H}}$. Because of this disassembly, ^{1}H NMR spectroscopy allowed determination of the molar ratio of $\mathbf{1_{2H}}$ to (*R*)-MA as 1:2.[12] These analytical data indicate that the leaf-shaped objects consist of a 1:2:2 ternary complex of $\mathbf{1_{2H}}$, $[Pt(dppp)]^{2+}$, and (*R*)-MA. This composition is the one expected for coordination polymer **3** (Scheme 2).

As there is no particular chiroptical feature of the ternary complex when it is dissolved in a good solvent such as CH_2Cl_2 (see before),[12] the $\mathbf{1_{2H}}$ units in the coordination polymer are, contrary to our expectation, hardly interlocked with one another configurationally. We rather assume if a prevailing one-handed helical array of $\mathbf{1_{2H}}$ must develop when the polymer assembles into the leaf-shaped object in acetone (Figure 1c). Consequently, the "majority rule" may operate in the individual polymer chains,[3–6] resulting in the amplified chiroptical response shown in Figure 2a (●). Hence, the next issue is to investigate whether the enantiomeric purity of $\mathbf{1_{2H}}$ in such assembled polymer chains is indeed amplified. Thanks to the chirality-memorizing ability of $\mathbf{1_{2H}}$ (see before), the polymer, upon treatment with DPPP-containing AcOH ($[DPPP]/[Pt^{II}] = 25$), dissociated into the monomer with retention of its configuration (Scheme 2). To confirm the validity of this evaluation protocol, a ternary mixture of $\mathbf{1_{2H}}$, (*R*)-MA, and $[Pt(dppp)]^{2+}$ was immersed in acetone at 20 °C for 12 h and then diluted by 300 fold with DPPP-containing AcOH. The chiroptical activity became less intense probably owing to disruption of the leaf-shaped assembly by depolymerization of the polymer into $\mathbf{1_{2H}}\cdot(AcOH)_2$.[12] However, this change gradually subsided, leaving an optically active species whose CD spectrum was virtually identical to that observed for the $\mathbf{1_{2H}}$/(*R*)-MA binary mixture post-treated in DPPP-containing AcOH. As the validity of the protocol was successfully confirmed, ternary mixtures of $\mathbf{1_{2H}}$, $[Pt(dppp)]^{2+}$, and (*R*)-MA of different *ee* values were prepared in acetone and poured into AcOH after immersion.[12] Again, the resulting $\Delta\varepsilon$ values of $\mathbf{1_{2H}}\cdot(AcOH)_2$ were nonlinear to the optical purities of MA with an upward convex dependency (Figure 2b, ●). For example, by using (*R*)-MA with only 20% *ee*, a $\Delta\varepsilon_{max}$ value, which is 62% as large as that observed with enantiomerically pure MA, was observed.[12] In contrast, the $\Delta\varepsilon$ values obtained from the $\mathbf{1_{2H}}$/MA binary mixtures after similar treatments showed a linear correlation with the *ee* values of the MA used (Figure 2b, ○). We likewise investigated the leaf-shaped objects, which were isolated from an acetone suspension of the ternary mixture with (*R*)-MA with only 10% *ee*. The $\Delta\varepsilon_{max}$ value, finally attained in DPPP-containing AcOH, was 39% as large as that with enantiomerically pure MA. This value agrees well with the one expected from the nonlinear $\Delta\varepsilon_{max}$/*ee* correlation in Figure 2b (●). Importantly, as confirmed by chiral HPLC, the *ee* value of MA in the leaf-shaped assembly (8% *ee* (*R*)) was virtually identical to that of added MA.[12] This result rules out the possibility that chiral amplification of $\mathbf{1_{2H}}$ is caused by the enantiomeric enrichment of MA in the leaf-shaped assembly. Taking into account all the above observations, we conclude that the observed chiral amplification originates from the "majority rule" operative in helical polymer **3** in the leaf-shaped assembly.

In summary, we have shown a new potential of helical polymers for amplified chiral transformations. The basic rationale of this concept, in principle, is not only limited to such supramolecular helical motifs but also can be elaborated into general asymmetric synthesis when appropriate helical scaffolds are designed.

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