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Assembly and Folding of Twisted Baskets in Organic Solvents

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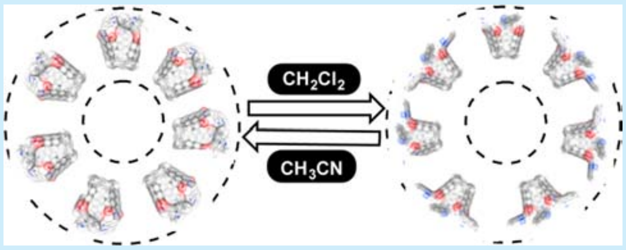
Supporting Information

ABSTRACT: A synthetic method for obtaining enantiopure and twisted baskets of type (*P*)-**3** is described. These chiral cavitands were found to fold quinoline gates, at the rim of their twisted platform, in acetonitrile and give molecular capsules that assemble into large unilamellar vesicles. In a less polar dichloromethane, however, cup-shaped (*P*)-**3** packed into vesicles but with the quinoline gates in an unfolded orientation. The ability of twisted baskets to form functional nanostructured materials could be of interest for building stereoselective sensors and catalysts.



Chemists have, in the last few decades, studied molecules within molecules[1] using cavitands and self-assembled capsules to explore ways toward (a) prolonging the lifetime of reactive intermediates,[2] (b) stabilizing transition states of chemical reactions,[3] (c) creating new forms of stereoisomerism,[4] (d) permitting crystallographic characterization of compounds,[5] (e) allowing detection of molecules,[6] and (f) controlling the outcome of chemical reactions.[7] In addition, folded aromatic oligomers[8] have also been examined for encapsulating molecules,[9] with their conformational dynamics affecting the rate by which guests enter/exit such structures.[10,11] As an example of a host possessing the characteristics of both foldamers and cavitands, calix[4]arenes with four cholic acids at the rim were found to fold the polar and nonpolar faces of cholates in response to the solvent polarity.[12,13] In this vein, we recently prepared so-called twisted baskets (Figure 1)[14] and used ^{1}H NMR spectroscopy to investigate the folding of hydrogen-bonded aromatic groups (gates)[11] at their rim (Figure 1A).[15] Importantly, the twisted framework of these baskets, with either a *P* or *M* sense of twist, was found to act as a chiral auxiliary and to transfer the stereochemical information to the folded gates by biasing them to assume a preferred unidirectional orientation.[15] Will the transfer of chirality and folding operate with large aromatic gates incapable of forming hydrogen bonds but with a propensity to "stack" in polar organic solvents (Figure 1B)?[16] To answer this question, we decided to prepare enantiopure basket (*P*)-**3** with quinoline gates (Figure 1B/C) and use exciton-coupled circular dichroism (ECCD)[17] to study its folding and chirality transfer.[18] Interestingly, enantiopure (*P*)-**3** assembles into vesicles in organic solvents.[19] The folding characteristics of the assembled hosts are a function of the solvent's polarity, but with no observed chirality transfer.

Recently, we developed a synthetic method for obtaining racemic (*P*/*M*)-**1** baskets (Figure 1C),[14] each possessing a bicyclo[3.2.1] hydrocarbon platform with a right- or left-handed sense of twist along with six methyl esters at the rim of the basket. The transesterification of (*P*/*M*)-**1** with (1*R*,2*S*,5*R*)-(−)-menthol gave diastereomeric (*P*)-**2** and (*M*)-**2**. Upon the separation of (*P*)-**2** from (*M*)-**2** with column chromatography, we assigned their absolute configurations with ECCD spectroscopy.[14] In the present study, we completed the resolution of racemic (*P*/*M*)-**1** via transesterification: strong acid CH_3SO_3H promoted the conversion of six (−)-menthol esters in (*P*)-**2** to yield enantiopure (*P*)-**1** as the hexamethyl ester (Figure 1C). The circular dichroism (CD) spectrum of (*P*)-**1** (blue, Figure 2) showed a negative CD couplet centered at 247 nm, in accord with the counterclockwise (−) position of three degenerate ^1B_b transitions from the naphthalene chromophores (Figure 2).[20] In particular, the positive Cotton effect (CE) at 239 nm ($\Delta\varepsilon_1 = 60$ M^{-1} cm^{-1}) is accompanied by a negative CE at 256 nm ($\Delta\varepsilon_2 = -112$ M^{-1} cm^{-1}) so that the *A* value for (*P*)-**1** ($|\Delta\varepsilon_1| + |\Delta\varepsilon_2| = 172$) is substantially smaller than for (*P*)-**2** (A = 536).[14] The interaction of naphthalene chromophores through space, as being a function of their distance (*d*) and orientation (Ω),[17] is evidently different for twisted hosts having the same sense of helicity (*P*) but with different esters at the rim. The inclusion of (−)-menthol in the cavity of (*P*)-**2**, as discerned in our prior work,[14] could certainly play a role in enhancing the rotational strengths of its bisignate spectrum.

To elucidate the folding characteristics of triimide (*P*)-**3**, we first completed its synthesis from enantiopure (*P*)-**1** (Figure 1C). In addition, we prepared (*P*)-**4** (Figure 1C) to carry "CD silent" *n*-butyl groups at the rim of its twisted platform. The CD spectrum of (*P*)-**3** in acetonitrile showed a negative CD couplet centered at 270 nm (red spectrum, Figure 3A). Presumably, the observed couplet originates from the interaction of $\pi-\pi^*$ transition dipole moments of the naphthalimide chromophores,[21] along each of their long axis and situated in the

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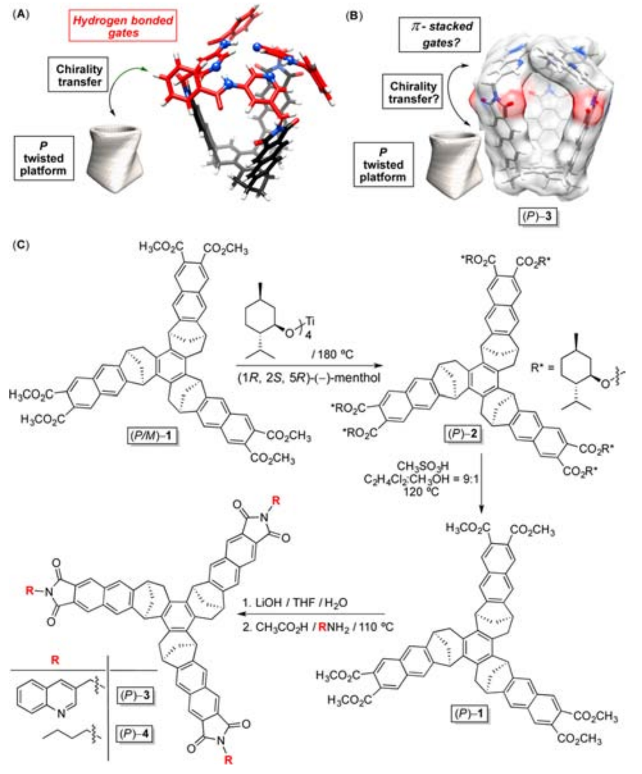

Figure 1. (A) Twisted basket with *P*-shaped cup and unidirectional amidopyridine gates at its rim forming a seam of N−H---N hydrogen bonds.[15] (B) Basket (*P*)-**3** with quinoline gates, π-stacked at its portal. (C) Resolution of racemic (*P*/*M*)-**1** as hexaesters. Chemical functionalization of (*P*)-**1** with aromatic and aliphatic amines gives triimides (*P*)-**3** and (*P*)-**4**.

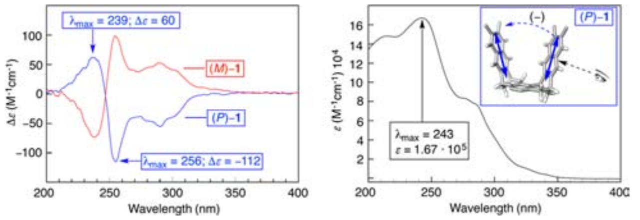

Figure 2. CD (left) and UV−vis (right) spectra of enantiopure (*P*)-**1** (blue, 10 μM) and (*M*)-**1** (red, 10 μM) at 298.0 K in CH_3CN. The coupling of $\pi-\pi^*$ transition dipole moments, along the long axis of each naphthalene chromophore at 247 nm, contributes to the observed negative CD couplets.

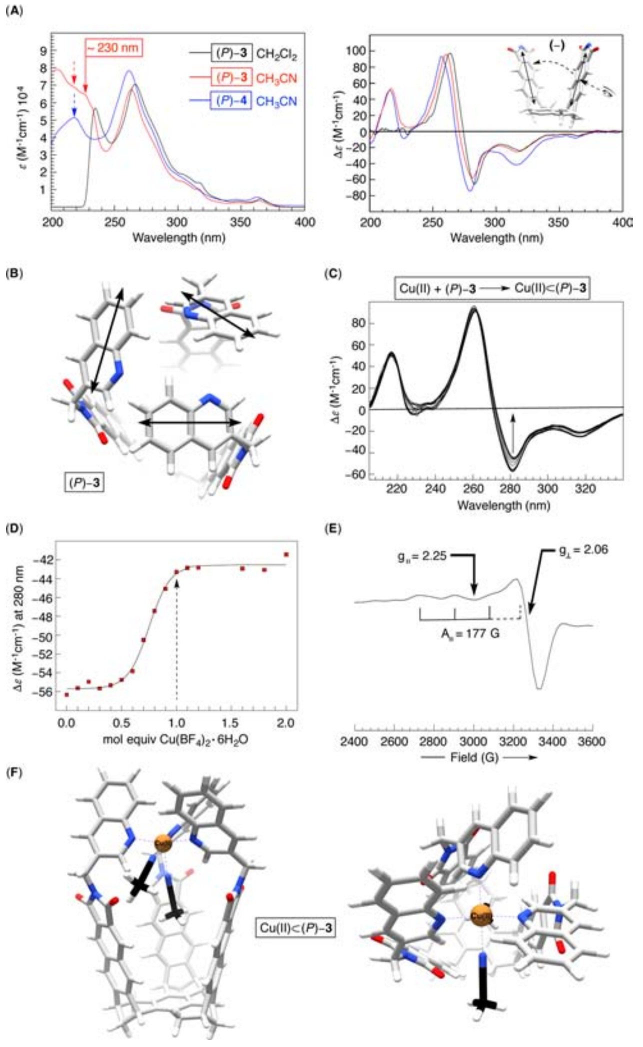

Figure 3. (A) UV−vis (left) and CD (right) spectra of (*P*)-**3** in CH_2Cl_2 (black, 10 μM) and CH_3CN (red, 10 μM) as well as (*P*)-**4** in CH_3CN (blue, 20 μM) at 298.0 K. (B) Top view of energy minimized (*P*)-**3** (MMFFs, Spartan), showing the transition dipole moments of quinolines. (C) Selected CD spectra of (*P*)-**3** in CH_3CN (20 μM, 298 K) obtained upon an incremental addition of a standard solution of $Cu(BF_4)_2{\cdot}6H_2O$ (1.0 mM) in acetonitrile. (D) Change in $\Delta\varepsilon$ (M^{-1} cm^{-1}) of a solution of (*P*)-**3** (20 μM) in acetonitrile at 280 nm, obtained upon an incremental addition of a standard solution of $Cu(BF_4)_2{\cdot}6H_2O$ (1.0 mM) in acetonitrile. (E) EPR spectrum of Cu(II)⊂(*P*)-**3** in CH_3CN at 100 K. A normal/axial EPR signature with equivalent *x* and *y* axes and two **g** tensor values ($\mathbf{g}_{II} = \mathbf{g}_z > 2.1 > \mathbf{g}_\perp = \mathbf{g}_x, \mathbf{g}_y > 2.0$ and $A = 177$ G) suggests a square-pyramidal coordination geometry about Cu(II). (F) Side and top views of square pyramidal Cu(II)⊂(*P*)-**3** (DFT: M06/6-31G*) showing the propeller-like orientation of three quinoline gates at the rim.

counterclockwise fashion (Figure 3A). In addition, the quinoline chromophores in (*P*)-**3** possess a transition electric dipole moment ($\lambda = 233$ nm, $\varepsilon = 57000$ M^{-1} cm^{-1}), polarized along each of their long axis (Figure 3B).[18] In line with it, we noted a complete absence of any Cotton effect or exciton coupling around 230 nm; the UV−vis spectrum of (*P*)-**3** reveals the presence of the quinoline chromophores (Figure 3A). Finally, the CD spectrum of (*P*)-**4** (Figure 3A) was in acetonitrile almost identical to the one corresponding to (*P*)-**3**. On the basis of the results, we presumed that three quinoline rings are (a) randomly situated about the rim of (*P*)-**3** in acetonitrile or (b) folded into left- and right-handed propellers to nullify the difference in the absorption of the circularly polarized light.

To additionally probe the conformational characteristics of (*P*)-**3**, we titrated a standard solution of $Cu(BF_4)_2{\cdot}6H_2O$ to this host in acetonitrile and monitored the process with CD spectroscopy (Figure 3C). In line with an earlier study,[18] the hypothesis was that the coordination of Cu(II) to the quinoline nitrogen atoms would join the aromatics and place them into a propeller like orientation (Figure 3F). The formation of a 1:1 Cu(II)⊂(*P*)-**3** complex was confirmed by a CD binding isotherm (Figure 3D) along with ^{1}H NMR spectroscopy (Figure S15) and mass spectrometry (Figure S16). In addition, the CD spectrum of Cu(II)⊂(*P*)-**3** was almost identical to the one corresponding to (*P*)-**3** (Figure 3C). The absence of an exciton couplet originating from quinolines (~230 nm) was

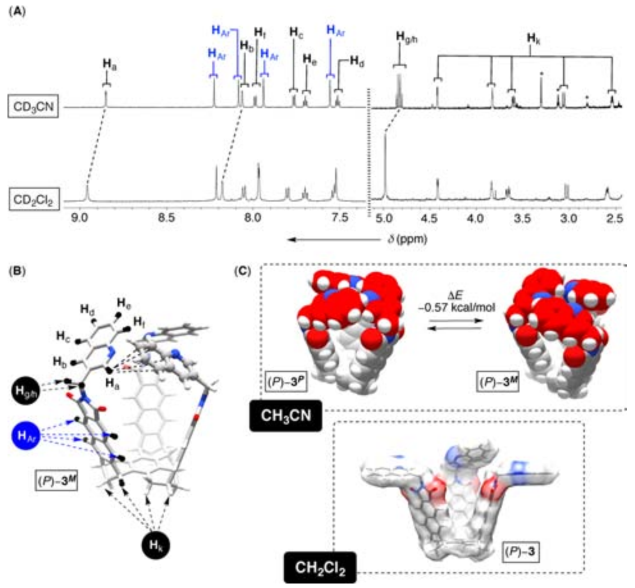

Figure 4. (A) Selected regions of ^{1}H NMR spectra (800 MHz, 298 K) of (*P*)-**3** in CD_3CN (50 μM) and CD_2Cl_2 (2.4 mM); residual solvent molecules are marked with star. (B) Assignment of proton nuclei in (*P*)-**3**. (C) Energy-minimized forms of (*P*)-**3** (DFT: M06-2X/6-31G*) with quinoline gates adopting helical *P*/*M* orientations (top) and randomly oriented about the rim (bottom).

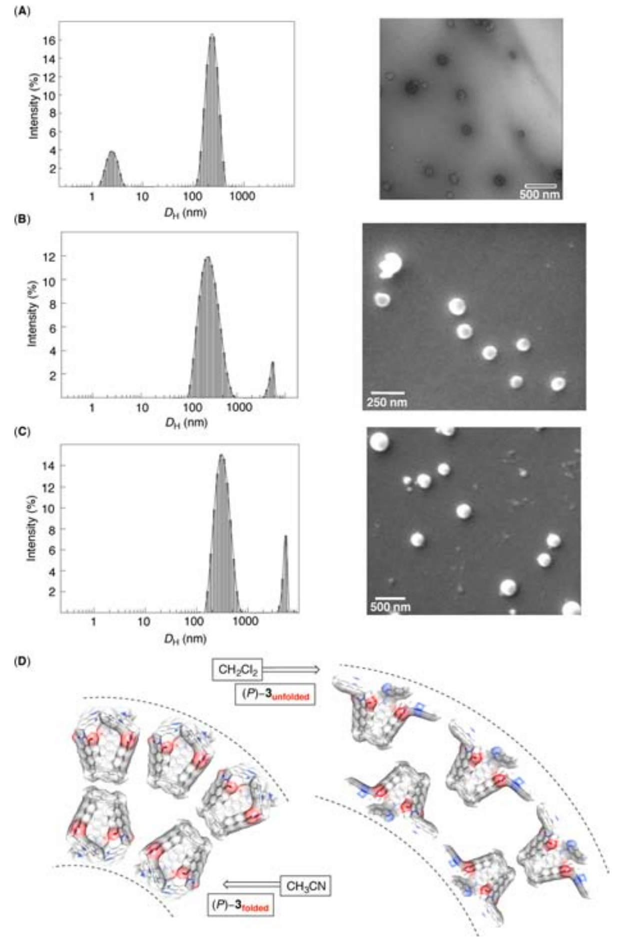

Figure 5. Results of DLS measurements of (A) 4.9 mM basket (*P*)-**3** in CH_2Cl_2, (B) 50 μM basket (*P*)-**3** in CH_3CN, and (C) 50 μM basket Cu(II)⊂(*P*)-**3** in CH_3CN at 298.0 K; note that for (A) comparable results were obtained for 50 μM (*P*)-**3** in CH_2Cl_2. (A) TEM image of (*P*)-**3** (50 μM in CH_2Cl_2) deposited on a copper grid and stained with uranyl acetate. (B, C) Scanning electron microscopy (SEM) images of (*P*)-**3** (50 μM in CD_3CN) and Cu(II)⊂(*P*)-**3** (50 μM in CD_3CN) deposited on a silicon wafer and coated with gold. (D) The proposed mode of packing of (*P*)-3 in CH_3CN (left) and CH_2Cl_2 (right) into vesicular membranes.

apparent despite the square-pyramidal coordination geometry of Cu(II)⊂(*P*)-**3** (Figure 3E)[22] in which the quinolines adopt *P*/*M* helical orientations (Figure 3F). On the basis of the results, we deduced that Cu(II)⊂(*P*)-**3** ought to have an interconverting population of right- or left-handed quinolines at top of its cavity with a limited (if any) bias on the gates' helicity!

Does basket (*P*)-**3** have similar folding characteristics as Cu(II)⊂(*P*)-**3**? As noted previously, aromatic oligomers are known to undergo a solvophobically driven folding in polar organic solvents (acetonitrile)[23] and unfolding in nonpolar solvents (dichloromethane).[16a] Accordingly, ^{1}H NMR spectra of (*P*)-**3** in CD_3CN and CD_2Cl_2 showed a set of resonances corresponding to, in each case, a C_3-symmetric molecule (Figure 4A/B); note that ^{1}H NMR spectrum of (*P*)-**3** in CD_2Cl_2 was invariant from 6.3 μM to 2.4 mM (Figure S9). We used cross-correlations, from two-dimensional ^{1}H−^{1}H COSY and NOESY spectra (Figures S10−13), to assign all of the signals. Notably, diastereotopic $H_{g/h}$ protons at the hinge position emerged as an AB quartet in CD_3CN (4.8 ppm, Figure 4A) while present as a singlet in CD_2Cl_2 (5.0 ppm, Figure 4A). In fact, our ^{1}H NMR data suggested a two-state transition upon the addition of neat CD_2Cl_2 to CD_3CN solution of (*P*)-**3** (Figure S14). To explain the observation, we invoked our recent results[15] in which the splitting of $H_{g/h}$ resonances into a quartet occurred with aromatic gates forming a unidirectional seam of hydrogen bonds but showing a singlet when the hydrogen bonds were broken. Accordingly, we deduced that the quinoline gates from (*P*)-**3** adopt clockwise and/or counterclockwise orientations in acetonitrile while remaining randomly oriented in dichloromethane (Figure 3C). The interpretation is also in line with the following computational and experimental results. First, energy minimizations (DFT: M06-2*X*/6-31G*)[24] of diastereomeric (*P*)-**3**, with *P* and *M* folded gates, revealed a small energy bias ($|\Delta E| = 0.57$ kcal/mol, Figure 4C) between diastereomers, thereby suggesting a comparable population of the two isomers ((*P*)-**3**^{M} and (*P*)-**3**^{P}). Second, the singlet corresponding to H_a from (*P*)-**3** was in CD_3CN (8.82 ppm, Figure 4A) found at a higher field than in CD_2Cl_2 (8.95 ppm, Figure 4A). To explain the observation, we note that each of the energy-minimized (*P*)-**3** structures places three aromatic gates at the top of the juxtaposed H_a protons (Figure 4B); in fact, these protons are less than 3.05 Å from the closest sp^2 hybridized carbon of the quinoline ring, i.e., within the cutoff distance for forming the attractive C−H---π interactions.[25] Thus, the anisotropic effect from quinolines is magnetically shielding H_a nuclei to reduce their chemical shift in acetonitrile, but not as much in dichloromethane. Third, the CD spectra of folded and unfolded forms of (*P*)-**3** are, in CH_3CN and CH_2Cl_2, almost identical (Figure 3A) and similar to Cu(II)⊂(*P*)-**3** in CD_3CN (Figure 3C); note that Cu(II)⊂(*P*)-**3** is insoluble in CH_2Cl_2. The observation is consistent with the notion that folded structures of (*P*)-**3** and Cu(II)⊂(*P*)-**3** (CH_3CN) have the quinoline rings residing both clockwise and counterclockwise at the rim to cancel their exciton coupling around 230 nm. The CD spectrum of the unfolded form of (P)-**3** (CH_2Cl_2) is, however, lacking the Cotton effects from its quinoline chromophores as these groups are residing further away from one another and also randomly oriented about the portal of the host.

Given low solubility of (P)-**3** in acetonitrile (micromolar range) and a broadening of its proton resonances in CD_2Cl_2 (Figure 4A), we decided to test if the aggregation of this host in organic media takes place. Accordingly, we completed a series of dynamic light scattering (DLS) and electron microscopy measurements of (P)-**3** in acetonitrile and dichloromethane (Figure 5). In line with the results, basket (P)-**3** assembled into spherical particles with the size distribution (diameters) centered at $D_H = 240$ nm in both CH_2Cl_2 (Figure 5A, PDI = 0.39) and CH_3CN (Figure 5B, PDI = 0.36). In addition, Cu(II)⊂(P)-**3** formed somewhat larger particles with hydrodynamic diameters centered at $D_H = 310$ nm (Figure 5C, PDI = 0.32). On the basis of the ability of amphiphilic and cup-shaped baskets to form vesicles in water,[26] we surmised that similarly shaped (P)-**3** assembles into a vesicular membrane in organic media in a comparable fashion (Figure 5D). That is to say, nonpolar and twisted cages pack in the interior of the lipid-like bilayer and away from bulk solvent with more soluble quinoline groups remaining in contact with solvent molecules.

In conclusion, we discovered that three quinoline gates on top of the twisted basket's cavity fold in acetonitrile by way of the solvophobic effect.[8a] In nonpolar dichloromethane, however, the quinolines unfold by assuming random positions about the rim. Importantly, both folded and unfolded baskets form nanosized vesicles in organic solvents. At present, we aim to employ the results of our findings for investigating the assembly of twisted baskets in water and promoting stereoselective recognition of complementary chiral molecules.[27]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01976.

Additional details of the experimental and computational protocols (PDF)

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Notes

The authors declare no competing financial interest.

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