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Chiral Calix[3]pyrrole Derivatives: Synthesis, Racemization Kinetics, and Ring Expansion to Calix[9]- and Calix[12]pyrrole Analogues

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Abstract: Chiral pyrrolic macrocycles continue to attract interest. However, their molecular design remains challenging. Here, we report a calixpyrrole-based chiral macrocyclic system, calix[1]furan[1]pyrrole[1]thiophene (**1**), synthesized from an oligoketone. Macrocycle **1** adopts a partial cone conformation in the solid state, and undergoes racemization *via* ring inversion. Molecular dynamics simulations revealed that inversion of the thiophene is the rate determining step. Pyrrole *N*-methylation suppressed racemization and permitted chiral resolution. Enantioselective *N*-methylation also occurred in the presence of a chiral ammonium salt, although the stereoselectivity is modest. A unique feature of **1** is that it acts as a useful synthetic precursor to yield several calix[*n*]furan[*n*]pyrrole[*n*]thiophene products (*n* = 2~4), including a calix[12]pyrrole analogue that to our knowledge constitutes the largest calix[n]pyrrole-like species to be structurally characterized.

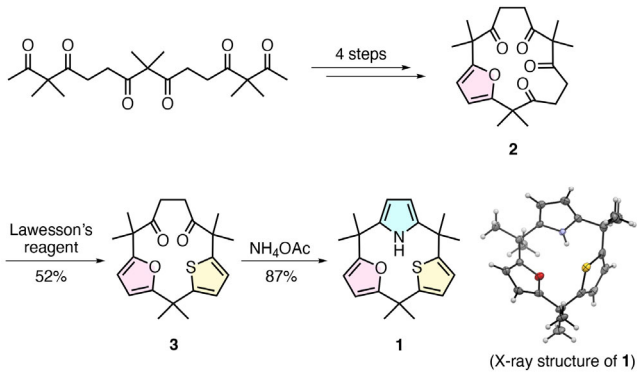
Chiral macrocycles have attracted considerable attention as possible scaffolds for stereoselective molecular recognition and for their potential chiroptical properties. This has made them targets of enantioselective syntheses.[1] In 1994, Böhmer introduced the term 'inherent chirality' for asymmetrically substituted calix[4]arenes in which no stereogenic center exists, but which display chirality as the result of belonging to the C_1 point group.[2] Currently, a variety of concave molecules, including cyclic amides,[3] phthalocyanines,[4] buckybowl molecules,[5] and metal complexes,[6] are recognized as being inherently chiral per this definition. Characteristic features of inherently chiral macrocycles are that i) racemization occurs upon macrocyclic ring inversion[7] and ii) that ring cleavage leads to achiral daughter products. In pioneering work, Wang and Tong synthesized chiral heteracalix[4]aromatics from achiral chains composed of four different aromatic rings with excellent enantioselectivity.[8] Very recently, Cai and co-workers employed asymmetric functionalization to generate inherently chiral analogues of calix[4]arenes.[9] However, the design parameters[10] leading to inherently chiral macrocycles are not yet well-established, in part because the energy barrier for ring inversion varies widely and in ways that are not always apparent. New, inherently chiral motifs could help narrow this knowledge gap. Here, we report a rational synthesis of the inherently chiral calixpyrrole analogue calix[1]furan[1]pyrrole[1]thiophene (**1**), an asymmetric heteroarene-containing calix[3]pyrrole analogue.

Calixpyrroles are pyrrole-containing calixarene analogues that have been extensively studied for their rich host-guest chemistry.[11] *Meso*-octamethylporphyrinogen, the parent form of calix[4]pyrrole, is known to change its conformation in the presence of guests.[12] Whereas the so-called 1,3-alternate conformation (in which two opposing pyrrole rings are pointing up and the other two are pointing down) is the most stable in the absence of a guest, the cone conformation is stabilized upon binding Lewis basic anion salts. Such conformational features might be considered favorable for the generation of inherently chiral macrocycles. However, ring flipping of the pyrrole rings in calix[4]pyrrole is so rapid in solution that the macrocycle shows time-averaged D_{4h} symmetry. This, in turn, renders calix[4]pyrroles effectively achiral (*i.e.*, mixture of enantiomers) even when substituents are introduced asymmetrically onto the pyrrole rings.

We recently reported the synthesis of calix[3]pyrrole, a contracted analogue of calix[4]pyrrole, obtained by subjecting a cyclic oligoketone to Paal–Knorr pyrrole ring-forming conditions.[13] Owing to the proximal arrangement of the three pyrroles, ring flipping is slower than in calix[4]pyrrole.[14] We thus envisioned that asymmetric ABC-type calix[3]pyrrole derivatives (where A, B, and C are different heteroarenes) would give an inherently chiral system whose dynamic motion, molecular recognition, and reactivity might differ from what is seen in either calix[3]- or calix[4]pyrrole. As a first foray into exploring this possibility, we have prepared calix[1]furan[1]pyrrole[1]thiophene

(**1**). While **1** slowly racemizes at room temperature in solution, *N*-methylation completely suppresses the racemization, enabling optical resolution of the pure enantiomers. In the presence of chiral cations, *N*-methylation occurs in an enantioselective fashion, albeit with modest *ee*. Compound **1** also acts as a useful synthetic precursor. Specifically, it undergoes acid-catalyzed ring cleavage and expansion to furnish calix[6]-, calix[9]- and calix[12]pyrrole-type macrocycles. The largest of these species was characterized by single crystal X-ray diffraction analysis and seen to adopt an achiral windmill-like conformation in the solid state.

The synthesis of **1** is summarized in Scheme 1. It proceeds through the furan-embedded macrocycle **2** that is, in turn, obtained from the linear trimer of 3,3-dimethylpentane-2,4-dione[15] in 4 steps.[14] One of the two 1,4-diketone moieties was then converted to a thiophene ring to give **3** in 52% yield by treating with 1.2 equiv of Lawesson's reagent. The remaining diketone unit was then subject to Paal–Knorr conditions to give **1** in 87% yield. The formation of **1** was confirmed by high-resolution electrospray ionization time-of-flight (ESI–TOF) mass spectrometric analysis, which revealed a parent cation peak corresponding to the sodium adduct [**1**+Na]$^+$ at *m*/*z* = 362.1545 (calculated for $C_{21}H_{25}NOSNa$, *m*/*z* = 362.1549). The ^{1}H NMR spectrum of **1** recorded in $CDCl_3$ revealed six signals assignable to the methyl protons between 1.4–1.8 ppm. The presence of multiple methyl peaks was taken as evidence that **1** is nonplanar and that flipping of the aromatic rings is slow on the NMR time scale. These methyl proton signals did not coalesce even at 150 °C in dimethyl sulfoxide-d_6 (DMSO-d_6). No obvious changes in the ^{1}H NMR spectrum were seen when **1** in $CDCl_3$ was subject to titration with tetrabutylammonium fluoride.



Scheme 1. Synthesis of inherently chiral macrocycle **1**.

A single crystal X-ray analysis revealed that **1** adopts a partial cone conformation in the solid state and conforms to the C_1 point group.[16] The thiophene sulfur atom points to the concave side, while the furan and pyrrole rings are directed to the convex side. The relative configuration in **1** was determined as (R_p^*,R_p^*,S_p^*) (the form shown in Scheme 1) with respect to the thiophene, furan, and pyrrole planes, respectively.

The relative energies of the eight possible stereoisomers for **1**, reflecting the planar chirality of each aromatic ring, were calculated at the B3LYP-D3/cc-pVTZ level of theory. Relative to the (R_p^*,R_p^*,S_p^*) form, the (R_p^*,S_p^*,S_p^*), (S_p^*,R_p^*,S_p^*), and (R_p^*,R_p^*,R_p^*) isomers were destabilized by 2.5, 2.8 and 2.9 kcal/mol, respectively (Supporting Information).

Chiral resolution of the two enantiomers of **1** was accomplished using an amylose-based chiral column and a mixture of *n*-hexane/*i*-PrOH (v/v = 1:1) as the eluent. While the two fractions exhibited almost mirror-image circular dichroism (CD) spectra, the signal intensity was relatively weak and diminished with time. We ascribe these findings to racemization *via* ring inversion post-separation. Curve fitting of the enantiomeric excess calculated from the peak area for each enantiomer in the high performance liquid chromatography (HPLC) chromatogram as a function of time using a first order kinetic model allowed the rate constant, *k*, and half-life, $t_{1/2}$, in hexane/*i*-PrOH (v/v = 1:1) to be estimated as 4.5×10^{-5} s^{-1} and 2.1 h, respectively (Figure 1). The activation enthalpy and entropy of racemization were determined to be ΔH = 76.6 kJ/mol and ΔS = –70.4 J/mol•K, respectively, from an Eyring plot analysis (Figure 1). The energy barrier of inversion (ΔG) at 298 K was thus calculated to be 97.6 kJ/mol, a value that is not sufficient to suppress completely racemization in solution at room temperature. The racemization rate of **1** proved solvent dependent; while the half-life in pure *n*-hexane was 2.5 h, those in CH_2Cl_2, MeOH, and *N,N*-dimethylformamide (DMF) were 1.7 h, 0.5 h, and 4.2 min, respectively.

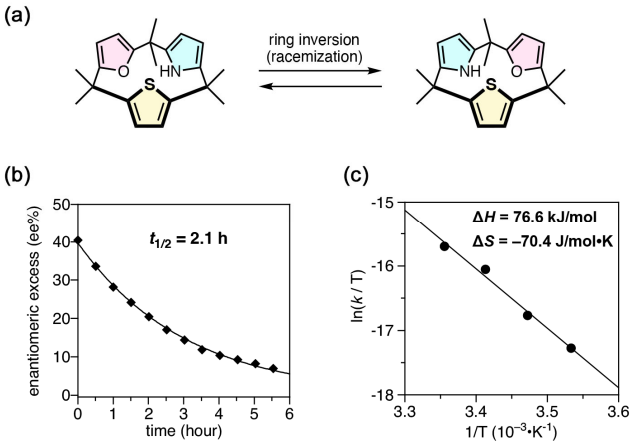


Figure 1. (a) Racemization of **1** *via* macrocyclic ring inversion. (b) Time-dependent decay of enantiomeric excess at 298 K in *n*-hexane/*i*-PrOH (v/v = 1:1). (c) Eyring plot for the racemization of **1**.

To gain further insight into the ring inversion, molecular dynamics (MD) simulations of **1** in *n*-hexane were performed for 25 ns. The distances between the heteroatoms d_X (X = N, O, and S) from the plane defined by the three *meso*-C-atoms plotted as a function of time are shown in Figure 2. As shown in a Supporting Movie, flipping of the pyrrole and furan rings occurred continually on this time scale, while only modest motion was seen for the thiophene subunit. During the MD simulation, the thiophene ring remained on one side of the macrocycle, leading us to suggest that inversion of the thiophene ring constitutes the rate determining step for racemization. Its relatively reduced motion may reflect the greater atomic weight of S vs O or N.

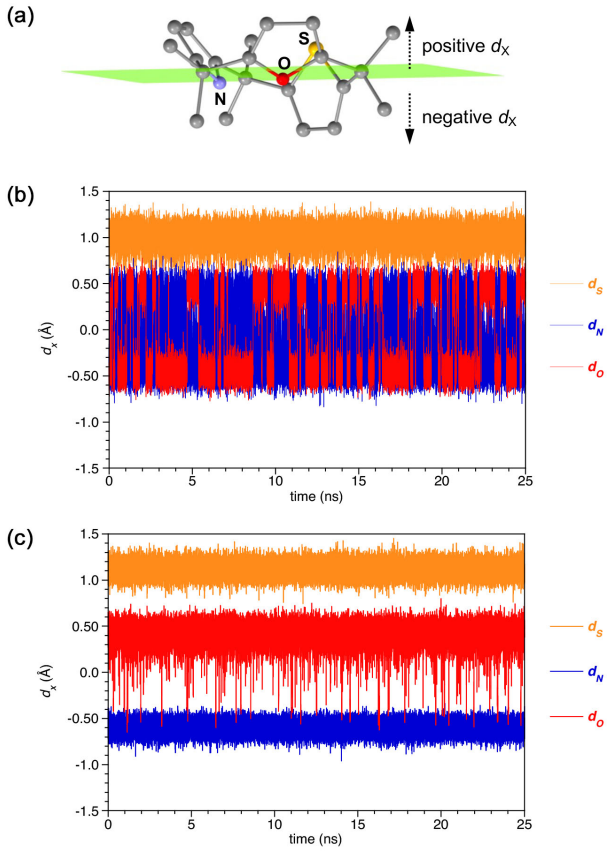


Figure 2. (a) Definition of distance, d_X (X = N, O, and S), with respect to the green plane defined by the three *meso*-carbon atoms. Plots of d_X as a function of time as seen in the MD simulation of (b) **1** and (c) **4**.

To suppress the racemization of **1**, we investigated the effect of structural modification by means of MD simulations. These analyses revealed that pyrrole *N*-methylation would serve to suppress pyrrole ring inversion over the full course of the simulation period (25 ns). Furan flipping also became sluggish as compared with **1** and thiophene flipping remained slow (Figure 2c, Supporting Movie S2).

In light of the above predictions, we prepared the *N*-methylated derivative **4** in 50% yield by treating **1** with methyl iodide and sodium hydride.[17] In fact, *N*-methylation allowed isolation of the two enantiomers of **4** in pure form after chiral resolution by HPLC using a cellulose-based chiral column (eluent: MeOH, at 40 °C, flow rate: 1.0 mL/min; retention times: 6.2 and 7.8 min, respectively).

The two enantiomers proved stable, with no detectable racemization being observed in MeOH at room temperature over the course of a month. Subjecting the first eluting fraction to recrystallization from CH_2Cl_2/MeOH allowed diffraction-grade single crystals to be obtained. The resulting structure (Figure 3) had a reasonable Flack parameter of 0.07(2) and revealed this enantiomer to have the (R_p,S_p,S_p) configuration with respect to the thiophene, furan, and pyrrole planes.[16] This structural analysis also confirmed that macrocycle **4** adopts a partial cone conformation in the solid state in analogy to what was seen for **1**. While the *N*-methyl group points toward the concave side, the sulfur and oxygen atoms were found oriented toward the convex side of the macrocycle, presumably to avoid steric repulsion with the *N*-methyl group.

The absorption spectrum of racemic **4** in *n*-hexane is characterized by a rather strong band at 240 nm and a broad band in the 270–320 nm spectral region. Observation of such red-shifted absorption features relative to the constituent heterocycles matches what was seen for other calix[3]-type macrocycles in which the close arrangement of aromatic moieties leads to presumed interchromophore interactions.[18] The CD spectrum of (R_p,S_p,S_p)-**4** was characterized by a positive signal at 254 nm and negative signals at 296 and 220 nm. As expected, its enantiomer, (S_p,R_p,R_p)-**4**, gave rise to a mirror-image CD spectrum. When photo-excited at 250 nm, compound **4** fluoresces at 373 nm and the overall emission spectrum mirrors the lowest energy absorption bands with a quantum yield of 0.06. Although subject

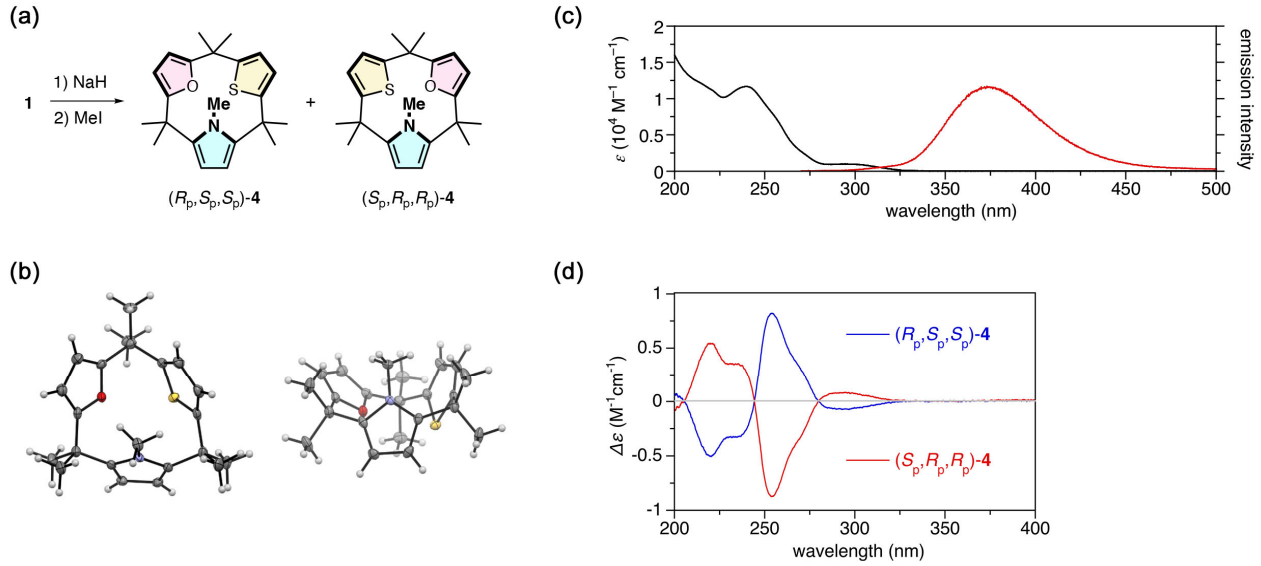


Figure 3. (a) Suppression of ring inversion by *N*-methylation of **1** to give **4**. (b) Single crystal X-ray structure of (R_p,S_p,S_p)-**4** (Left: top view, Right: side view). (c) Electronic absorption (black line) and fluorescence emission (red line; excited at 250 nm) spectra of racemic **4** in *n*-hexane. (d) CD spectra of (R_p,S_p,S_p)-**4** and (S_p,R_p,R_p)-**4** in *n*-hexane.

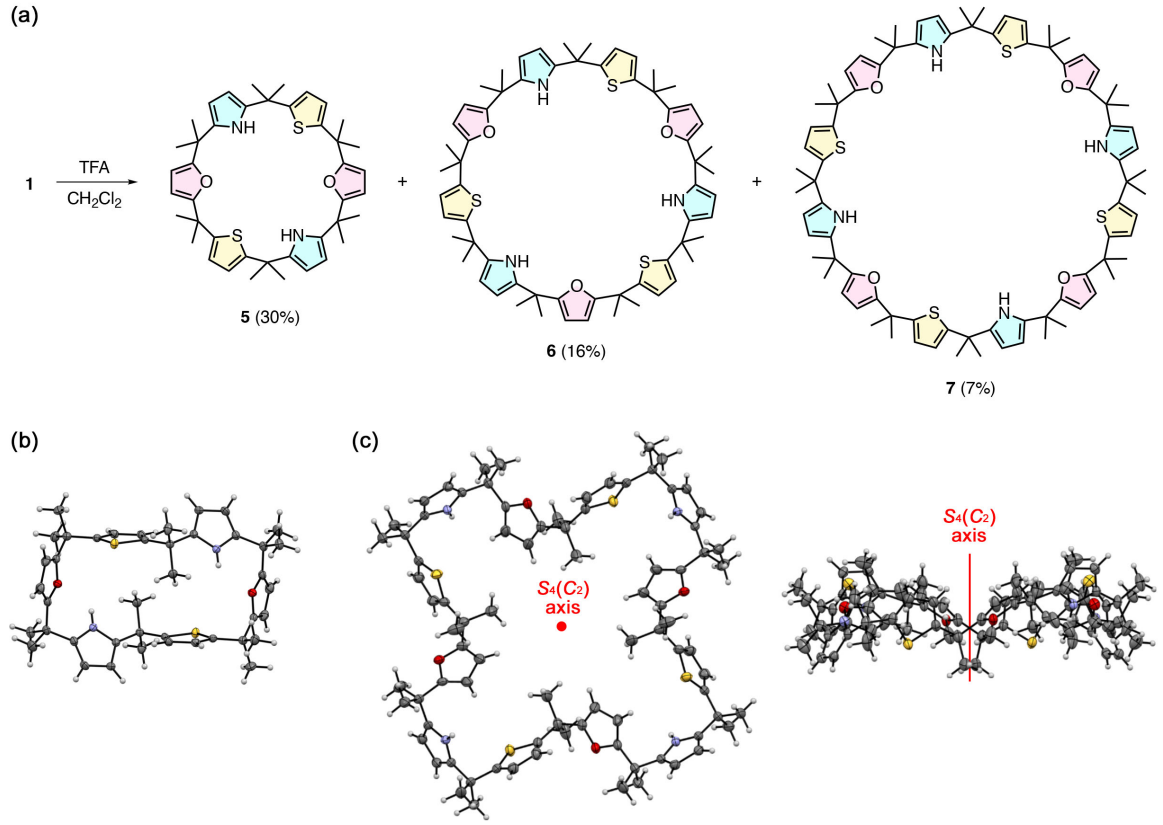


Figure 4. (a) Ring expansion reaction of **1**. X-ray crystal structures of (b) **5** and (c) **7** (left: top view, right: side view). (O: red, N: light blue, S: yellow, C: grey, H: white) Solvent molecules are omitted for clarity.

to a circularly polarized luminescence analysis, no signals were observed for enantiomerically pure **4**.

Given the chiral features of **1**, we considered that it might allow for enantioselective molecular recognition and could be specifically applied to effect the dynamic kinetic resolution of enantiomers. To test this possibility, **1** was subject to *N*-methylation in the presence of chiral ammonium salts. After deprotonation of the NH proton with sodium hydride, **1** was treated with (*R*)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1',2'-e]azepinium bromide[19] in DMF to exchange the counter cations. When the reaction solution was further treated with methyl iodide, (R_p,S_p,S_p)-**4** was obtained in 48% yield with 10% ee. Although the stereochemical conversion is modest with this and other chiral salts (cf. Supporting Information), this result indicates that the inherent chirality of **1** can be transferred to an appropriately chosen substrate. It thus supports the earlier finding that the conformational motion of **1** may be locked by increasing the inversion energy barrier *via* *N*-methylation.

Calix[3]pyrroles are known to undergo strain-induced ring expansion to give calix[6]pyrrole-type macrocycles *via* linear intermediates.[14] We therefore explored the reactivity of **1**. Treatment of **1** with trifluoroacetic acid (TFA) gave larger macrocycles analogous to **1**, namely, calix[2]furan[2]pyrrole[2]thiophene (**5**), calix[3]furan[3]pyrrole[3]thiophene (**6**), and calix[4]furan[4]pyrrole[4]thiophene (**7**), in 30%, 16%, and 7% yield, respectively (Figure 4 and Supporting Information). As observed for calix[1]furan[2]pyrrole,[14] the ring expansion reaction of **1** proceeded in a regioselective fashion, with no evidence of other positional isomers being seen by NMR spectroscopy. However, in contrast to calix[3]pyrrole and calix[1]furan[2]pyrrole, which in our hands give calix[6]pyrrole-type macrocycles exclusively upon ring expansion, calix[1]furan[1]pyrrole[1]thiophene (**1**) was found to support formation of the calix[9]- and calix[12]pyrrole analogues **6** and **7**. It thus appears to act as a useful synthetic precursor that allows access to large calix[n]pyrrole-type macrocycles that have been the targets of previous synthetic campaigns but not, to our knowledge, ever structurally characterized.[20]

Single crystal X-ray analysis of **5** and **7** revealed that both species are achiral.[16] Macrocycle **5** adopts a rectangular conformation and exists in the C_i point group as observed for other calix[6]pyrrole analogues.[21] In contrast, the calix[12]pyrrole analogue **7** exists in a windmill-like conformation in which the same furan→pyrrole→thiophene sequence is repeated four times. Structural analysis revealed that **7** falls in the S_4 point group and is thus achiral despite the absence of a mirror plane or inversion center. Attempts to separate enantiomers of macrocycles **5**–**7** using various conditions proved unsuccessful. Moreover, no changes in the ^{1}H chemical shifts or a coalescence / splitting in the signals was seen when compounds **5**–**7** were subject to VT-NMR spectral analysis from -60 to 40 ºC in $CDCl_3$. Such findings are consistent with the expectation that ring inversion in **5**–**7** is relatively fast rendering them effectively achiral. This stands in contrast to **1**, where the small ring size and associated ring inversion constraints serve to slow conformational motion. As

noted above, this motion can be further slowed *via* *N*-methylation to give **4**.

In conclusion, we designed and synthesized two inherently chiral macrocycles based on the calix[3]pyrrole motif. While calix[1]furan[1]pyrrole[1]thiophene **1** slowly racemized at room temperature, pyrrole *N*-methylation (to give **4**) effectively suppressed ring inversion, allowing chiral resolution of the individual enantiomers. MD simulations revealed that inversion of the thiophene and *N*-methylpyrrole subunits constitute the likely rate determining steps for **1** and **4**, respectively. The dynamic nature of **1** was harnessed to achieve the enantioselective synthesis of **4** through salt metathesis with a chiral ammonium salt, albeit only in modest *ee*. Acid catalyzed ring expansion of **1** allowed access to larger calix[3*n*]-type macrocycles as achiral daughter products. Included among these latter species was a calix[12]pyrrole analogue that, to our knowledge, constitutes the largest structurally characterized calix[*n*]pyrrole reported to date. Taken in concert, the present study highlights the promise calix[3]pyrrole-type macrocycles hold as inherently chiral frameworks and how fine-tuning their structure *via* functionalization (*N*-methylation in the present instance) can serve to control the dynamics of ring inversion-based racemization. Calix[3]pyrrole analogues, such as the ones reported here, also hold promise as unique synthetic intermediates. Further explorations of their inherent chirality and reactivity features are thus ongoing in our laboratories.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Chirality • Macrocycles • Calixarenes • Racemization kinetics • Ring expansion

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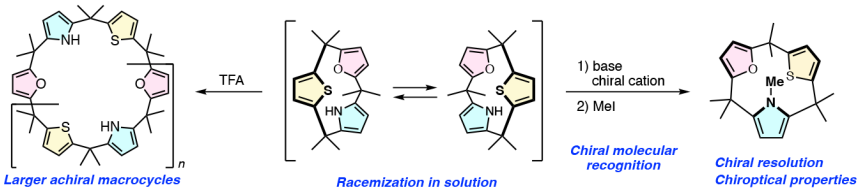

An inherently chiral calix[3]pyrrole derivative was synthesized from a polyketone precursor. Although the macrocycle racemizes through ring inversion at room temperature, *N*-methylation effectively suppressed the racemization, allowing chiral resolution of the enantiomers. Ring expansion reaction allowed access to calix[9]- and calix[12]pyrrole-type macrocycles, the largest of which was characterized by an X-ray diffraction analysis.

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