Control of Aromatic Ring Inversion in Calix[3]pyrrole

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Inversion of aromatic rings in macrocyclic compounds such as calixarenes or calixpyrroles can dynamically change their conformations and alter their reactivity, host-guest interactions, and chirality. In this work, we investigated aromatic ring inversion behaviors of calix[3]pyrrole[1], a ring contracted analogue of calix[4]pyrrole, and its derivatives.

Pyrrole ring inversion in calix[3]pyrrole **1** was rapid in solution to be observed as a time averaged C_3 symmetric molecule in ^{1}H NMR spectrum (**Fig. 1a**). Upon binding of fluoride anion, **1** adopts cone-like conformation to have hydrogen-bonds with fluoride efficiently. When two pyrrole rings of **1** were replaced with furan and thiophene rings to give **2**, its nonplanar conformations became chiral. Though two enantiomers of **2** were separated by chiral HPLC and exhibited mirror-image CD spectra, **2** underwent racemization via aromatic ring inversion in *n*-hexane/*i*-PrOH (v/v = 1/1) at room temperature with a half-life of 2.1 hours at 298 K (**Fig. 1b**). When **2** was methylated at NH site to give **3** in 50% yield, aromatic ring inversion was effectively suppressed. Enantiomers of **3** were successfully separated using chiral HPLC, and no racemization was observed for over a month at room temperature. The crystal structure of one of the enantiomers showed partial cone conformation that can be assigned as (R_p, S_p, S_p) with respect to thiophene, furan, and pyrrole plane respectively (**Fig. 1c**). This difference in racemization behaviors between **2** and **3** were applied for chiral recognition during *N*-methylation using chiral ammonium salt.

Furthermore, when the ring inversion in **1** was inhibited in its boron complex **4** (**Fig. 1d**), a drastic change was observed in its reactivity towards acids. While **1** caused rapid ring cleavage upon treatment with TFA, boron complex **4** showed amphophilic behavior with the macrocycle withstanding acidic conditions by reversible protonation at pyrrole ring.

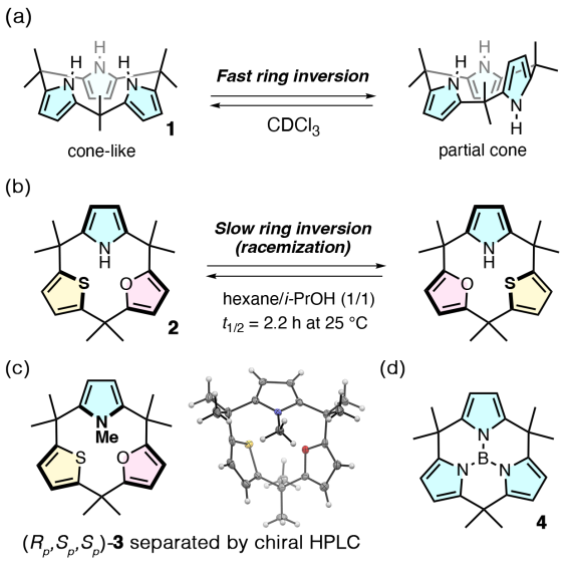

Fig. 1. (a) Pyrrole ring inversion in **1**, (b) aromatic ring inversion-based racemization of **2**, (c) molecular and crystal structure of (R_p, S_p, S_p)-**3** separated by chiral HPLC, and (d) molecular structure of **4**.

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