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AN OPTICALLY ACTIVE CYCLOOCTATETRAENE INCAPABLE OF RACEMIZATION

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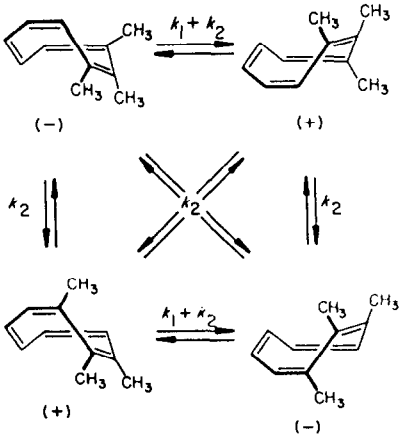
Summary: Cycloheptene-1,2-dicarboxylic anhydride has been transformed into the 1,4-annulated cyclooctatetraene **1**, which in turn was resolved via its diastereomeric *endo*-bornyltriazolinedione Diels-Alder adducts; **1** did not racemize during 23 hours at 158°C.

The capability for ring inversion (RI) and bond shifting (BS) is fundamental to the cyclooctatetraene (COT) ring system.[1] Extensive theoretical[2] and experimental investigations[3] over many years attest to the significance of this phenomenon as it relates to our understanding of $4n$ π electronic character. In recent years, proximal peripheral substitution of the COT nucleus has emerged as a very powerful tool for evaluating the energetics of RI and BS in [8]annulenes, especially in chiral examples.[4] The heightened vicinal steric perturbation reduces the ease of planarization within these carbocyclic frameworks and permits isolation of bond shift isomers in enantiomerically pure form. 1,2,3-Trimethylcyclooctatetraene constitutes a representative example. On warming, racemization occurs by RI (k_1, nonexchange of ring positions) and/or BS (k_2, site exchange) and the operation of these pathways can be individually assessed.



The present goal was the first synthesis of a cyclooctatetraene incapable of racemization. To construct a COT of this level of conformational rigidity, it becomes important to introduce structural features that

not only prevent planarization of the [8]annulene core, but other possible racemization schemes as well. These include transannular bonding with formation of bicyclo[3.3.0]-octadienediyl biradicals,[5] pseudorotational flexing about the fluted perimeter, and any other topological change leading to loss of optical activity.

Hydrocarbon **1** suggested itself as a suitable target because its pentamethylene loop was expected to preclude passage of the ethylenic fragment through its confines. Furthermore, bond shifting is certain to engender a substantial increase in ring strain. Also, the location of the methyl substituent, while necessary for disrupting C_s symmetry, also appeared to guarantee against the loss of enantiomeric purity via the other imaginable mechanistic schemes.

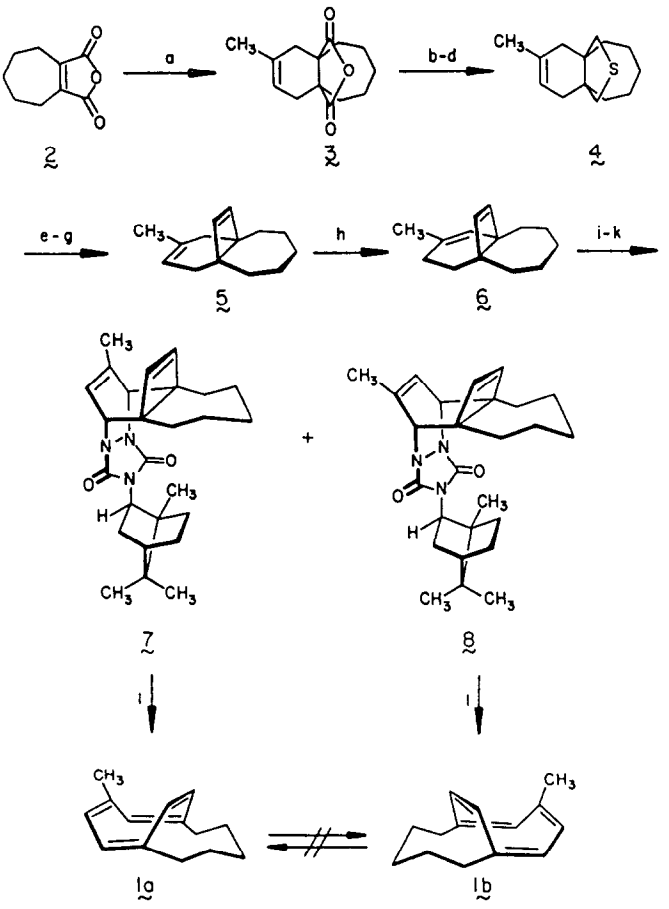
Anhydride **3**, the product of Diels-Alder addition of isoprene to **2**[6] (dioxane, 170°C, 68 h, 71%), already contains all of the requisite carbon atoms. Conversion of **3** to sulfide **4** proceeded smoothly (78% overall). In preparation for Ramberg-Bäcklund rearrangement,[7] **4** was α-chlorinated and chemoselectively oxidized (45%). Exposure of the epimeric α-chloro sulfone mixture to potassium *tert*-butoxide in tetrahydrofuran at -78°C afforded **5** (61%).[8]

Because all attempts to dehydrogenate **5** uniformly met with failure,[9] advantage was taken instead of the unexpected ease with which its isomerization to **6** occurs in the presence of 48% hydrogen bromide at 20°C (86%). Once migration of the double bond was achieved, it became possible to brominate the allylic ring methylene position regioselectively and to effect the desired dehydrobromination with sodium methoxide in tetrahydrofuran. The annulated cyclooctatetraene produced in this manner (34%) was directly condensed with enantiomerically pure (-)-*endo*-bornyl-1,2,4-triazolinedione.[10]

Partial separation of **7** from **8** was made possible by HPLC on a Waters Prep 500 instrument using peak shaving and recycling techniques. Diastereomeric excesses of 46% and 50% were realized for the pair of urazoles (^{1}H NMR analysis at 300 MHz).[11,12] Whereas hydrolysis-oxidation of the less polar adduct, $[\alpha]_D^{22}$ -27.9° (*c* 0.94, C_2H_5OH), gave **1** (88%) exhibiting $[\alpha]_D^{20}$ -33.7° (*c* 0.16, diglyme), comparable treatment of the more polar urazole, $[\alpha]_D^{22}$ +14.1° (*c* 0.77, C_2H_5OH) furnished the enantiomeric [8]annulene, $[\alpha]_D^{20}$ +29.0° (*c* 0.21, diglyme). Their ^{1}H NMR spectra [(300 MHz, $CDCl_3$) δ 5.86 (s, 2 H),

5.73 (s, 1 H), 5.62 (m, 1 H), 5.58 (s, 1 H), 2.38-2.30 (m, 2 H), 2.17-1.96 (m, 2 H), 1.93-1.82 (m, 2 H), 1.80 (s, 3 H), 1.49-1.16 (m, 4 H)] were superimposable.

Two experiments were now carried out simultaneously. A solution of racemic **1** in diglyme-d_{14} was sealed into an NMR tube to permit periodic spectral scrutiny. A second solution of optically active **1** in diglyme was prepared to monitor any change in $[\alpha]_D$ with time. Following the sequential heating of these solutions at 74.6°C (126 h), 83.2°C (36 h), and 94.6°C (24 h), no measurable change was noted by either criterion. An increase in temperature to 158°C (22.3 h) promoted a 7% drop in optical activity, corresponding strictly to a comparable level of decomposition to unidentified by-products.



[a]$CH_2=C(CH_3)CH=CH_2$, dioxane, hydroquinone, 170°C, 68 h. [b]$LiAlH_4$, THF. [c]CH_3SO_2Cl, py, 0°C. [d]Na_2S, HMPA, 130°C, 20 h. [e]NCS, CCl_4, reflux, 1 h. [f]Monoperphthalic acid, ether, -78° → 0°C. [g]KO*t*Bu, THF, -78° → 0°C. [h]48% HBr, EtOAc, RT, 4 h. [i]NBS, AIBN, CCl_4, reflux 10 min. [j]$NaOCH_3$, THF, RT, 3 days. [k](-)-*endo*-bornyltriazolinedione, EtOAc, RT, 3 days. [l]NaOH, $(CH_3)_2CHOH$, 75-80°C, 36 h; NH_4OH; MnO_2, ether.

Thus, dynamic conformational behavior must be severely curtailed in **1**. This previously unobserved phenomenon preserves the homochiral nature of its enantiomers until the onset of thermally induced destruction (perhaps by air oxidation). We view **1** as an extreme case. The question of whether less stringent architectural features might permit the controlled racemization of [8]annulenes is currently under active study.[13]

References and Notes

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(8) All new compounds described herein gave correct elemental analysis and/or accurate mass spectral data. All ^{1}H NMR, ^{13}C NMR, and IR spectra are also in accord with the assigned structures.

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(12) Efforts to ascertain the absolute configuration of **7** or **8** (and thence (+)-**1** and (-)-**1**) by X-ray crystal structure analysis continue.

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