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BARRIERS TO RING INVERSION IN DIBENZO[a,c]CYCLOOCTENE AND ITS DIHYDRO AND TETRAHYDRO DERIVATIVES BY RACEMIZATION AND NMR BANDSHAPE STUDIES

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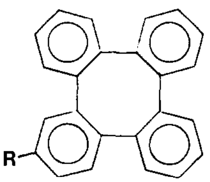
Abstract: Dibenzo[a,c]cyclooctene and its 9,10-dihydro and 9,10,11,12-tetrahydro derivatives have been resolved by chromatography and their inversion barriers determined by thermal racemization. The 9,12-dihydro derivative has been studied by ^{1}H NMR bandshape technique.

Dynamic NMR spectroscopy is a valuable technique for study of the dynamics of cyclic systems, but it fails when the barriers are higher than ca. 25 kcal/mol. In chiral cyclic molecules, ring inversion is often an enantiomerization process, which can be followed by thermal racemization of the individual enantiomers, and in this way processes with higher barriers may be studied. The advent of efficient chromatographic techniques for enantiomer resolution has made available a large number of chiral compounds in optically active form. Chromatography on swollen microcrystalline triacetylcellulose (TAC)[2-6] has proven very valuable for preparative enantiomer resolution, also for pure hydrocarbons. Thermal racemization monitored by the change in intensity of the CD spectrum has been found a useful technique, with good sensitivity and permitting observation if new optically active compounds should be formed in the process.[7]

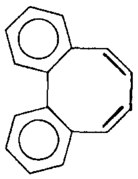
Several years ago, one of us[8] estimated the inversion barrier in tetrabenzocyclooctene (<u>1a</u>) to 120 kcal/mol by simple strain energy calculations, and later Gust et al.[9] could show by demonstrating optical stability of the monocarboxylic acid <u>1b</u> for 36 h at 251 °C that the inversion barrier was > 45 kcal/mol. We have resolved the acetyl derivative <u>1c</u> by chromatography on TAC, but it is not stable enough at 250 °C to permit a racemization study. Clearly, it would be of great interest to study the ring inversion in dibenzo[a,c]cyclooctene (<u>2</u>), which possesses only one unfavourable H-H interaction in the transition state.

This molecule has been shown by X-ray crystallography to be chiral and have nearly C_2 symmetry.[10]

We have used chromatography on TAC to resolve dibenzo[a,c]cyclooctene (2) and its 9,10-dihydro and 9,10,11,12-tetrahydro derivatives (3 and 5), and we have studied their thermal racemization, which is also the ring inversion. The 9,12-dihydro (4) derivative could not be resolved at room temperature, but we have studied its dynamic behaviour by ^{1}H NMR.



1 a, R = H
b, R = CO_2H
c, R = $COCH_3$



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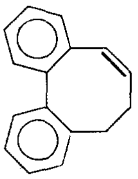

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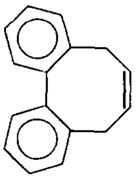

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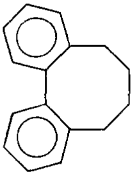

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Compound (2) was prepared according to Sondheimer and Wong.[11] Passage of 2.4 mg in 1 ml of ethanol through a TAC column[4] gave complete enantiomer separation (R_s = 5.75), the first eluted enantiomer (E_1) having $\alpha_{367} > 0$, CD spectrum (λnm/$\Delta\varepsilon$) 267/+16.7, 227/+38.1, 202/-90.4. The racemization was followed by heating samples ($4.3 \cdot 10^{-4}$ M in spectrograde ethanol) in sealed ampoules in a thermostat at 102° for different times and recording their CD spectra after rapid cooling. This gave $\Delta G^{\ddagger}$ (racemization) = 29.5 kcal/mol, and $\Delta G^{\ddagger}$ (inversion) = 30.0 kcal/mol, which agrees with the recent report by Heinz *et al.*[12] that 10-isopropyl-(2) does not show temperature-dependent NMR spectra.

9,10-Dihydrodibenzo[a,c]cyclooctene (3) was prepared by reaction of 4 with N-bromosuccinimide followed by reduction with $LiAlH_4$ to give a 35:65 mixture of 2 and 3. The mixture was resolved by preparative HPLC on a silica column with pentane as the mobile phase. Pure 3 has hitherto not been described, but it has been reported in mixture with 4.[13,14] Racemic 3 has m.p. 109-110 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): H9, H9′, δ 2.59 (m) and 2.92 (m); H10, H10′, δ 2.41 (m) and 2.72 (m); H11, δ 5.65 (m); H12, δ 6.37 (m); H1-H8 δ 7.28 (m). ^{13}C NMR ($CDCl_3$, 75 MHz); δ 30.81, 33.17; 125.86, 126.48; 127.02; 127.69; 127.74; 128.42; 128.65; 129.17; 129.98; 130.16; 137.82; 139.12; 140.68; 142.07, the latter four being resonances of quaternary carbon atoms. Racemic 3 was readily resolved by chromatography on TAC (R_s = 3.70, E_1: $\alpha_{367} > 0$) CD: 249/-8.83, 231.5/+11.61, 222/-2.27/, 207/+81.8.

The racemization of 3 was performed in a water-jacketed CD cell, held by thermostat at +49.0 and +64 ^{o}C, by following the intensity of the strong 207 nm band, giving $\Delta G^{\ddagger}_{rac}$ = 24.1 ± 0.1 kcal/mol and $\Delta G^{\ddagger}_{inv}$ = 24.5 ± 0.1 kcal/mol.

9,12-Dihydrodibenzo[a,c]cyclooctene (4) was prepared according to Ref. 11. The benzylic proton resonance appears as an AB system modified by residual coupling when the olefinic protons are decoupled, and coalescence at 120 ± 5 ^{o}C corresponds to $\Delta G^{\ddagger}_{inv}$ = 19.5 ± 0.3 kcal/mol.

9,10,11,12-Tetrahydrodibenzo[a,c]cyclooctene (5) was prepared by catalytic (Pd/C) hydrogenation of the mixture of 2 and 3. Injection of 6 mg in 1 ml of ethanol on the TAC column gave good enantiomer separation (R_s ca. 3.7), but the trace of the UV detector did not return to baseline between the peaks, indicating slow racemization on the column. The E_1 fraction ($\alpha_{367} > 0$) showed a CD spectrum with a positive maximum at 234 nm and a stronger one at 217 nm, and a strong negative maximum at ca. 201 nm. Monitoring the intensity of the 217 nm band at +27 and +41 ^{o}C gave $\Delta G^{\ddagger}_{rac}$ = 22.8 kcal/mol, $\Delta G^{\ddagger}_{inv}$ = 23.2 kcal/mol, in reasonable agreement with $\Delta G^{\ddagger}_{rac}$ = 23.2 kcal/mol found by Dvorken *et al.*[15] for the corresponding 10,11-dicarboxylic acid.

The parent eight-membered ring, *cis,cis*-1,3-cyclooctadiene was studied by Anet and Yavari[16] by low-temperature ^{1}H and ^{13}C NMR and by molecular mechanics calculations, and they found that the molecule can adopt two conformations, a twist boat-chair (TBC) with C_2 symmetry and a twist boat (TB) form without symmetry elements, 0.5 kcal/mol higher in energy. Both forms are *a priori* possible for 5, but Gottlieb *et al.*[17] concluded, based on studies of substituted derivatives, that the TBC form dominates strongly. We found the 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra to agree with C_2 symmetry and to be unchanged in the range +25 to -80 ^{o}C. The ^{1}H NMR spectrum (in $(CCl_3)_2CO$) consists of a complex multiplet for the aromatic protons and a doublet of doublets at δ 2.55 (H9, H12), and triplets at 2.06 (H9′, H12′), 1.94 (H10, H11) and 1.40 (H10′, H11′). When the temperature is increased, all signals broaden considerably from +160 ^{o}C, but they are still far from coalescence at +190 ^{o}C.

Our data for 5, although in harmony with an exclusive TBC form, which racemizes by inversion of the biphenyl unit, cannot exclude the presence of the TB form in rapid equilibrium with the TBC form even at -80 ^{o}C. However, MMP2 calculations[18] gave the TBC and TB forms as energy minima with the former more stable by 2.9 kcal/mol. We will continue this study by an ^{1}H NMR investigation at lower temperature and by further molecular mechanics calculations.

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