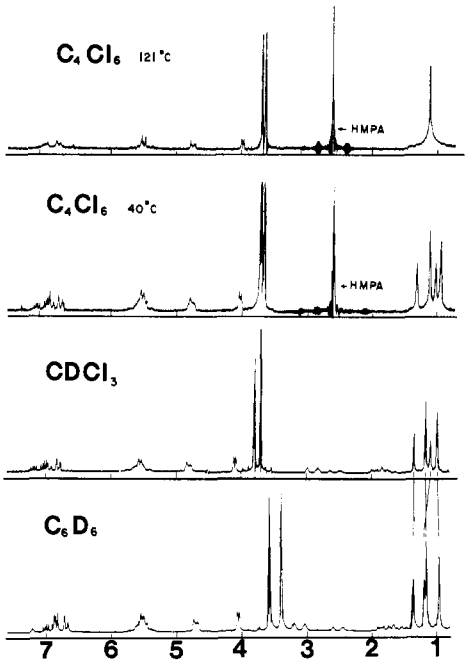
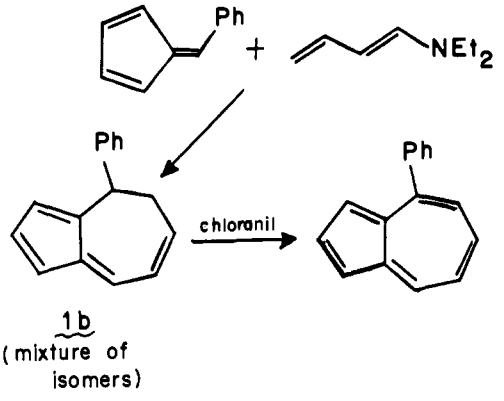


Figure 2. NMR spectra of the mixture of conformational isomers, **2** and **2'**.

Scheme II



and 1.17, while those in the minor isomer appeared at δ 1.23 and 1.38. That these isomers were conformational and not structural is demonstrated by both the similarity of the spectra of the isomers, and by the temperature dependent NMR spectrum of this mixture. At 120 °C (in hexachlorobutadiene), the four methyl singlets apparent at room temperature collapse to a single sharp resonance. The methoxy resonances collapse into two sharp singlets at 60 °C, while the remaining resonances simplify as expected. Cooling the sample results in restoration of the original spectrum. Steric considerations and the chemical shifts of the methyl groups in the two isomers in $CDCl_3$ and C_6D_6 lead to the tentative conclusion that **2** is the more stable conformer.

This relatively high barrier to conformational inversion ($\Delta G^{\ddagger}$ estimated as 18–20 kcal/mol from coalescence temperatures) is probably the consequence of the quaternary center attached to the bridgehead. Dibenzobarrelenes with quaternary carbons attached to bridgeheads show even larger barriers.[9]

The potential of this reaction in the synthesis of azulenes is demonstrated by the sequence of reactions beginning from 6-phenylfulvene (Scheme II). Reaction of 6-phenylfulvene with 1-diethylaminobutadiene (1:1) in CCl_4 for 1 day, followed by MeI workup and column chromatography, gave, in 62% yield, a mixture of dihydroazulenes, as indicated by the complexity of the NMR spectrum. Reaction of 1 g of this mixture with chloranil in refluxing xylene for 15 min gave royal blue 4-phenylazulene (110 mg) after silica gel chromatography. The spectroscopic properties of this compound (uv, ir)[10,11] are identical with those of the authentic material.

The general availability of fulvenes from cyclopentadienes and ketones, and of dienamines from α,β-unsaturated carbonyl compounds, along with the simple workup procedures required for these reactions, indicate that this procedure may provide a useful alternative to the related Hafner azulene synthesis,[12] which utilizes an electrocyclization analogous to the cycloaddition reported here.

Returning to the theoretical impetus for this work, our preliminary results with the less electron-rich 1-methoxybutadiene system indicate that only powerfully nucleophilic and nonelectrophilic 4π systems such as 1-diethylaminobutadiene (ionization potential (IP) = 6.96 eV; electron affinity (E.A.) ~ -2 eV) and diazomethane (I.P. = 9.03 eV, E.A. ~ -1.5 eV) will react with alkyl or aryl fulvenes in a [6 + 4] sense. However, fulvenes substituted at the 6-position by electron-withdrawing groups are expected to show this behavior more generally. These reactions, and the generality of the azulene synthesis, are subjects of continuing investigations.

Acknowledgment. We are grateful to the National Science Foundation, the National Institutes of Health, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research.

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Bond Fixation in Annulenes. 4. The Ability of 1,2,3-Trimethylcyclooctatetraene to Support Optical Activity[1]

Sir:

Incremental introduction of double bonds into medium-sized rings so alters the interplay of nonbonded interactions that widely divergent ground state conformational preferences frequently result. Cyclooctane and its derivatives, for example, appear to exist predominantly in boat-chair or crown conformations[2] while cyclooctatetraenes (COT's) are decidedly tub-shaped.[3] Understandably, the dynamics of conformational mobility must differ significantly in the two families. As con-

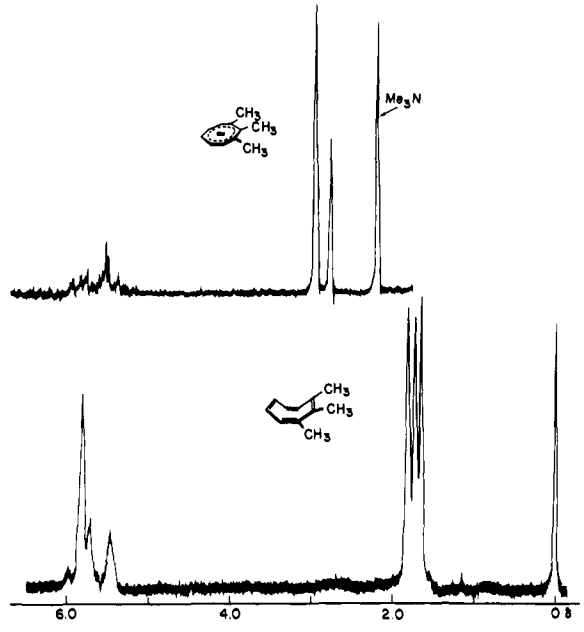
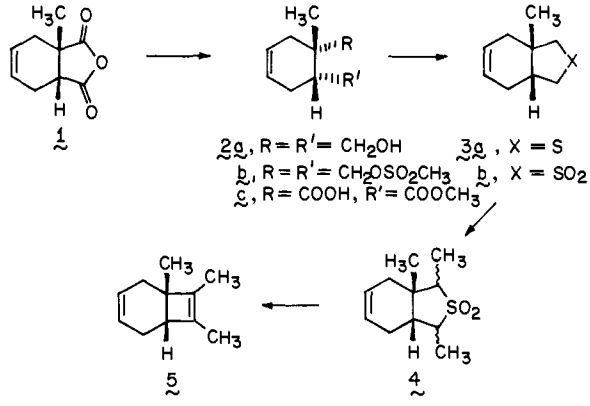


Figure 1. ^{1}H NMR spectra (60 MHz) of: (bottom) 1,2,3-Me_3COT (**6**) in $CDCl_3$; (top) dipotassio 1,2,3-trimethylcyclooctatetraenide (**10**) in ND_3 at −55 °C (Me_3N present as internal standard, δ_{Me_4Si} 2.135).

cerns cyclooctyl systems, an appreciation of both strain-energy contributions and single bond rotational parameters have recently acquired rather quantitative sophistication.[4] In contrast, those factors which contribute to bond shifting (BS)[5] and ring inversion (RI)[6] in COT's are less well understood.[1,7-9] We now show that 1,2,3-Me_3COT can support optical activity and that the ability of its [8]annulene core to undergo BS and RI is seriously impeded by this low degree of ring substitution.

Lithium aluminum hydride reduction of **1**[10] in THF yielded diol **2a** which was efficiently converted in turn to dimesylate **2b**, cyclic sulfide **3a**, and sulfone **3b** by established procedures.[1,9b] This sulfone was dimethylated by sequential treatment



with 2 equiv of *n*-BuLi in THF at −80 °C and excess methyl iodide. The resulting crude product, which consisted chiefly of **4** (^{1}H NMR analysis), was dissolved in anhydrous dioxane, treated at 0 °C with 1 equiv of *n*-BuLi, and introduced via syringe into a refluxing slurry of $LiAlH_4$ in dioxane.[11] Subsequent distillation gave ring contracted diene **5** (30%) as a colorless oil: $\delta_{Me_4Si}^{CCl_4}$ 5.75-5.45 (m, 2 H), 2.40-1.70 (m, 5 H), 1.70-1.32 (m, 6 H), and 1.17 (s, 3 H).[12] Bromination of **5** with 1 equiv of Py·HBr_3 resulted in electrophilic attack at the cyclohexene double bond. Dehydrobromination of this intermediate with LiCl and Li_2CO_3 in anhydrous HMPA (90 °C, 20 h)[13] led to a transient bicyclo[4.2.0]octatriene, its immediate disrotatory ring opening affording title compound **6** (69%). The room temperature 60-MHz ^{1}H NMR spectrum (in $CDCl_3$) of this COT (Figure 1) consists of three distinct

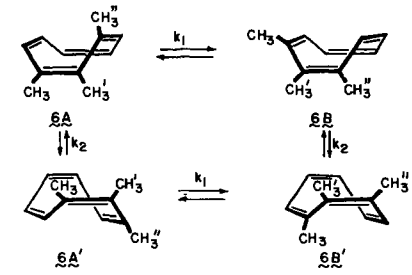


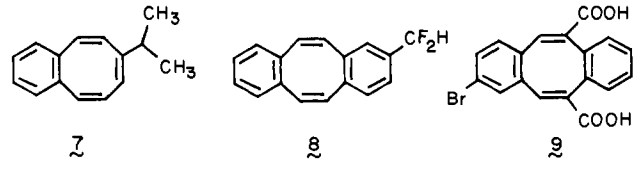
Figure 2. Kinetic scheme for bond shifting and ring inversion in **6**. The possibility of concurrent BS and RI processes has not been explicitly considered.

methyl singlets at δ 1.80, 1.72, and 1.64 in addition to a vinyl proton multiplet of area 5 at 6.00-5.35. At 90 MHz in Me_2SO-d_6 solution, the methyl signals are shifted downfield to δ 2.80, 2.71, and 2.63, respectively. As the temperature of such solutions was gradually increased to a maximum of +190 °C,[14] no coalescence of the singlets due to the outer methyl groups (CH_3 and CH_3'') was observed, although slight broadening was evident. The environments of these two substituents are therefore not experiencing meaningful exchange at this temperature as they must be if BS were occurring (Figure 2). A lower limit to the barrier for the **6A** ⇄ **6B** and **6A'** ⇄ **6B'** interconversions is therefore 27 kcal/mol. In actuality, the true value is quite probably considerably higher.[15]

Elucidation of the ease of ring inversion in **6** required its availability in optically active form. For this purpose, acid ester **2c**, mp 116-118 °C, was prepared by methanolysis of **1**. Efficient resolution of **2c** could be accomplished with *endo*-bornylamine and a highly purified sample, $[\alpha]^{25}D$ −13.8° (*c* 10.8, EtOH),[16] was transformed in the predescribed manner through **3b***, $[\alpha]^{25}D$ +45.2° (*c* 12.5, CH_2Cl_2), and **5***, $[\alpha]^{25}D$ +140.9° (*c* 12.7, pentane), to **6*** with presumably undiminished optical purity. The highest specific rotation realized to date for the dextrorotatory enantiomer of this dissymmetric cyclic polyolefin is $[\alpha]^{25}D$ +20.2° (*c* 6.0, pentane).

Thermal activation studies on (+)-**6**, conducted in Pyrex ampoules at 160 ± 0.5 °C in diglyme solution, resulted in first-order racemization. The specific rate constant for loss of optical activity in the recovered samples of **6*** (k_2 in Figure 2) was determined by the method of least squares to be (7.8 ± 0.2) × 10^{-4} s^{-1}. Through application of the Eyring equation, a $\Delta G^{\ddagger}$ value of 31.7 kcal/mol was calculated as the ring inversion barrier at this temperature.

That the transition state for interconversion of **6A** with **6A'** (or **6B** ⇄ **6B'**) is notably destabilized can perhaps be best gauged by comparison with other COT's for which quantitative data are available. In simple monosubstituted derivatives, ring inversion barriers do not exceed 15 kcal/mol,[6,8c] a feature which also prevails in mono- and dibenzo fused derivatives such as **7** ($\Delta G^{\ddagger}$ = 13.4 kcal/mol at −30 °C)[8c] and **8** ($\Delta G^{\ddagger}$ = 12.3 kcal/mol at −5 °C).[8e] Only when additional carboxyl groups are introduced as in **9** does the enantiomerization process attain a level of kinetic retardation somewhat comparable (E_{act} = 27 kcal/mol)[8a] to that found in **6**.



The diminished conformational flexibility encountered in **6**, the simplest COT yet to be resolved, is clearly due to the presence of a triad of methyl groups. The strong nonbonded repulsive interactions which come into play as planarity de-

velops[5-7] contribute significantly to destabilization of the BS and RI transition states. That the steric impact of three-CH_3 groups is seemingly more effective in this regard than the contiguous tetrasubstitution arrangement in **9** is intriguing and may mean that geometric arrangements other than the accepted planar alternate form can lead to mechanical tub-to-tub inversion. Work is in progress to gain further insight into this question.

From the finding that **6** experiences ready reduction to **10** with K in ND_3, we see that the aromaticity of this dianion is adequate to offset the prevailing steric destabilization. The symmetry of **10** as revealed by its ^1H NMR spectrum (Figure 1) is consistent with a planar formulation. The polarographic half-wave potential for 2ϵ transfer to **6** ($E_{1/2} = -2.20$ V vs. SCE, anhydrous HMPA solution) can be related to the values obtained for the 1,2-me_2 (−1.95 V), 1,2,3,8-Me_4 (−2.43 V), and 1,2,3,4-Me_4 (−2.54 V) homologues.[1] In this instance, a direct quantitative correlation between the facility of reduction and anticipated ease of ring flattening is evident.

Acknowledgment. The authors wish to thank the National Science Foundation for financial support as well as G. D. Ewing and S. G. Traynor for their role in the dianion generation and electrochemical reduction studies, respectively.

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(14) As a result of such prolonged heating, decomposition of the sample was noted when 200 °C was reached.
(15) Attempts to ascertain a more accurate estimate of the bond shift barrier by suitable methyl group labeling is in progress.
(16) That essentially complete resolution had been achieved was established by conversion of **2c** to its acid chloride (oxalyl chloride, C_6H_6, 0 °C, 30 min) and subsequent reaction with d-(+)-α-methylbenzylamine. The resulting amide, $[\alpha]^{25}D$ +66.5° (*c* 18.8 EtOH), exhibits a single methyl ester absorption (δ 3.59) with no sign of the second signal which is present (ratio 1:1) when racemic **2c** is similarly treated (δ 3.59 and 3.66).
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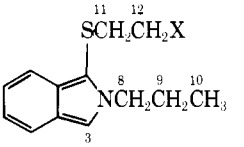
The Structure of the Fluorescent Adduct Formed in the Reaction of *o*-Phthalaldehyde and Thiols with Amines

Sir:

Several reagents are currently available for the fluorogenic detection of amino acids and proteins.[1,2] The reaction of these substances with *o*-phthalaldehyde (OPTA) and β-mercaptoethanol (MERC) is particularly attractive since the strongly fluorescent product allows smaller amounts of amino acids to be detected than is possible by other methods.[2] The full potential of the OPTA reaction has not yet been realized, however, nor can it be realized without a knowledge of the chemical structure of the adducts. In this communication we present evidence that the fluorescent OPTA reaction products are 1-alkylthio-2-alkyl-substituted isoindoles (e.g., I).



Ia, X = OH
Ib, X = H

Primary amines in general, in addition to amino acids and proteins,[2] react with OPTA and MERC to yield the same type of fluorescent products as indicated by thin layer chromatographic and uv and fluorescence spectral analysis.[3] Furthermore, the hydroxyl group of MERC is not essential for the reaction.[3] We thus chose *n*-propylamine and ethanethiol (ET), in addition to MERC, for our studies since they should present fewer chemical problems and simplify the task of structural elucidation. While the fluorescent adducts could not be isolated, solutions of the desired material could be readily prepared in at least 90% purity, when analyzed by NMR and thin layer chromatography. Mass spectral analysis of a solution containing the OPTA/MERC/*n*-propylamine product implicated a compound constructed from 1 equiv of each reactant minus 2 equiv of water. An exact mass determination gave $C_{13}H_{17}NOS$ as the only possible composition of the parent ion (obsd = 235.1033; calcd = 235.1031). Furthermore, the observed and calculated ions of the four major fragmentation peaks agreed to within 0.5 mmu.

The structure Ia was deduced from the infrared spectrum, which exhibited a broad OH band but no carbonyl or SH band, and from the proton NMR spectrum of the total reaction mixture (Figure 1). The large downfield shift of the N-CH_2 group and the integration of the signals at 6.8–7.8 ppm indicated that nitrogen had become part of a five proton aromatic ring system. A consideration of the structure of the starting materials and the negligible shift of the S-CH_2 group suggested attachment of the sulfur atom to what was most likely an isoindole ring system. Finally 2 equiv of water, predicted by the mass spectral analysis as being a side product of the reaction, were observed at 2.9 ppm (Figure 1). The NMR spectrum of the fluorescent ET adduct Ib yielded similar results and allowed a definitive assignment of the nonaromatic protons of Ia (C_8 at 4.30, C_{11} at 2.68, C_{12} at 3.50 ppm). Examination of the aromatic region in both spectra revealed a 2:1:2 proton pattern. The low field, two proton multiplet was assigned to the C_4 and C_7 protons. The signal at 7.31 ppm (1 H) is observed as a barely detectable doublet ($J \simeq 0.75$ Hz), as expected for the C_3 proton. No detailed proton NMR study of isoindoles has been reported but theoretical considerations predict a chemical shift pattern and assignment identical with that of Figure 1.[4]

The isoindole structure of I explains why secondary amines do not yield fluorescent products in the reaction with OPTA.[2]