magnitude of the geometrical changes which were permitted in any one iteration.

The bending and stretching force constants for cyclohexane are given in Table I. It is not possible to obtain a unique set of constants in this case because the six bond angles about a carbon are not independent. Further, the C–C stretching modes are coupled with angle bending. As a result, the two quite different sets of force constants, 1 and 2, both lead to a reasonably small rms deviation between calculated and observed vibrational frequencies. The calculations for bicyclo[3.1.1]heptane were carried out using the methylene force constants given in set 2, along with the cyclobutane force constants summarized in Table IV.

The equilibrium geometry for cyclohexane[18] was taken as $\theta$(CCC) = 111°, $\theta$(HCC) = 109.5°, and $\theta$(HCH) = 107.9°; that for cyclobutane[19] was taken as $\theta$(CCC) = 90°, $\theta$(HCC) = 113.9°, and $\theta$(HCH) = 110°. The torsional interaction and nonbonded interaction functions suggested by Boyd[9b,c] were used. The former was set to correctly represent the barrier to rotation about the $C_2$–$C_3$ bond of ethane and the latter adapted from functions derived by Williams[20] from crystalline hydrocarbon data.

Table IV. Force Constants for Bicyclo[3.1.1]heptane

| Internal coordinate[a] | $k$, mdyn/Å[b] | Internal coordinate[a] | $k$, mdyn/Å[b] |
|---|---|---|---|
| C′–C | 3.57[c] | H–C–C′ | 0.677 |
| C′–H | 4.69 | H–C′–C | 0.65[c] |
| C′–C′ | 2.85 | H–C′–C′ | 0.636 |
| C–C–C′ | 1.336 | H–C′–H | 0.393 |
| C–C′–C′ | 0.8[c] | | |
| C′–C′–C′ | 0.762 | | |

[a] C refers to a carbon in a cyclohexane ring and C′ refers to a carbon in a cyclobutane ring. [b] The force constants for the cyclobutane ring were derived from a vibrational analysis for $C_4H_8$ and $C_4D_8$ using only the diagonal force constants (ref 11). [c] Estimated value.

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# 1-Hydroxy- and 1-Oxo[2.2]metacyclophane. Optical Resolution and Ring Rotation

**Heinz W. Gschwend**

*Contribution from the Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901.*
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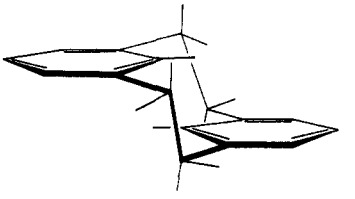
**Abstract:** The synthesis and optical resolution of 1-oxo[2.2]metacyclophane and the equatorial and axial isomers of 1-hydroxy[2.2]metacyclophane are described. One antipode of the ketone was transformed *via* reduction, thermal equilibration, and oxidation into its mirror image. The kinetic parameters for the ring inversion of 1-hydroxy[2.2]metacyclophane were determined by measuring the rates of their respective thermal equilibration: equatorial isomer, $\Delta H^{\pm} = 29.6 \pm 1.7$ kcal/mol, $\Delta S^{\pm} = -8.5 \pm 4.0$ eu, $\Delta G^{\pm}_{150} = 33.2$ kcal/mol from $k_2$ values; axial isomer, $\Delta H^{\pm} = 31.7 \pm 1.7$ kcal/mol, $\Delta S^{\pm} = -2.75 \pm 4.0$ eu, $\Delta G^{\pm}_{150} = 32.9$ kcal/mol from $k_1$ values. At 151.5° the equilibrium constant was found to be $K = 1.49$ for equatorial/axial. The kinetic parameters for the ring inversion of 1-oxo[2.2]metacyclophane, accessible by measuring the rates of racemization, were determined to be: $\Delta H^{\pm} = 10.75 \pm 0.19$ kcal/mol, $\Delta S^{\pm} = -48.4 \pm 0.6$ eu, and $\Delta G^{\pm}_{150} = 25.05$ kcal/mol. A hypothesis for the extremely large negative entropy term and thus the transition state is discussed.

For many years various research groups have been attracted by the chemistry and the spectral properties of the [2.2]metacyclophane skeleton **1**.[1,2] Its conformation, which was elucidated by X-ray measurements,[3] is apparently frozen into a chair-like nonplanar form. This very feature allows the possibility of preparing chiral structures simply by introducing substituents into the aromatic rings in a manner that destroys the plane of symmetry bisecting the unsubstituted [2.2]metacyclophane. Molecules with such inherent asymmetry have in fact been prepared[4] and reports have appeared on the optical resolution of 4,14-dimethyl[2.2]metacyclophane.[5] Another way to produce



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chiral metacyclophanes is in the introduction of substituents on the ethano bridge; this too has been realized in the syntheses of 1,2-dimethyl[2.2]metacyclophane ($CH_3$ groups cis)[6] and isomeric mixtures of 1,9(and 1,10)-bismethylsulfido[2.2]metacyclophane.[7] Chiral [2.2]metacyclophanes appear to be ideal sub-

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(2) D. J. Cram, *Accounts Chem. Res.*, 4, 204 (1971).
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(4) S. Akabori, T. Sato, and K. Hata, *J. Org. Chem.*, 33, 3277 (1968).
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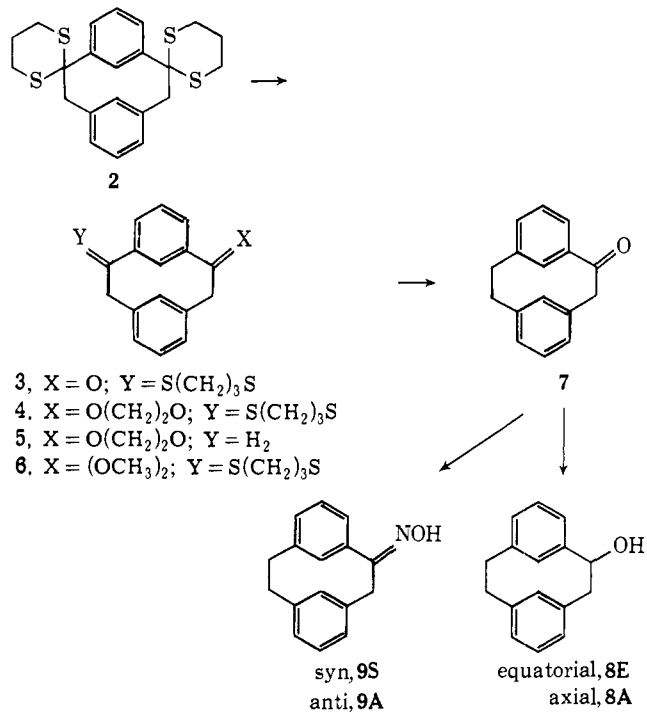
strates for the determination of the ring inversion barrier, *i.e.*, the transformation of one chair conformer into its mirror image. Although optically active [2.2]-metacyclophanes have been prepared[5] nothing is reported on a conceivable thermal racemization. However, high-temperature nmr studies have been carried out[5,8] on **1** and up to temperatures of 200° no inversion, that is, no coalescence, of the nonequivalent methylene protons was observed. Whereas the conformational changes of the [2.2]furanophane and [2.2]-2,6-pyridinophane analogs of **1** can be observed by the signal coalescence of the $CH_2$ protons at much lower temperatures (63 and 13.5°)[9] the activation energy for ring inversion of **1** has been estimated at more than 27 kcal/mol.[5b,8] Similarly, it was found that with [2.2]metacyclo-2,6-pyridinophane[10] and the thiophenophane and furanothiophenophane[11] no signal coalescence occurred up to 200°. Consequently, accurate determinations of these energy barriers which lie beyond the time scale limited capability of the nmr technique have to be carried out on the real time scale by using chiral substrates. 1-Hydroxy- and 1-oxo[2.2]metacyclophane should allow the study of the thermal equilibration of diastereoisomers and the racemization, respectively.

## Synthesis

Among the various approaches available for the construction of the [2.2]metacyclophane skeleton[1,2] the one described by Boekelheide and coworkers[12] was the method of choice for the target ketone **7**. The known first step involving alkylation of the dianion of isophthalaldehyde bis(1,3-propanedithioacetal) with *m*-xylylene dibromide was markedly improved utilizing the dilution principle. Yields of 64–71% before chromatography (reported, 28%[12]) were consistently and reproducibly obtained and considerable quantities of **2** accumulated. The yields realized by this method are, to our knowledge, higher than those of any other one-step synthesis of the metacyclophane skeleton, and also represent an impressive demonstration of the utility of the lithiodithiane method in C–C bond formation.[13] Selective reduction of the diketone, derived from **2**,[12] to an isomeric mixture of keto alcohols was accomplished, but all attempts to transform such products into **7** or **8** were unsuccessful. However, selective deketalization of **2** with $HgCl_2$ in 2:1 dioxane–water gave access to the useful monoketone **3**, which was separated in 42% yield from starting material (26%). The ratio of the two solvents is very critical for this optimal yield, and none of the other solvent systems tried for this reaction (*e.g.*, $CH_3OH$–$H_2O$ or THF–$H_2O$) gave even traces of **3** but only produced the diketone. Possibly *p*-dioxane plays an active role in this step, such as acting as a bidentate ligand complexing with $Hg^{2+}$. The resultant steric effects might be the cause for the selective removal of only one of the ketal groups. The structure of ketone **3** is firmly established by its ir (Nujol, 1700 $cm^{-1}$) and nmr spectrum: the two protons adjacent to the carbonyl group appear as an AB system at 2.48 and 3.43 ppm ($J_{AB}$ = 13 Hz). The internal aromatic protons appear at 4.9 ($H_8$) and 5.6 ppm ($H_{16}$). The latter one is deshielded by one of the sulfur atoms, an effect which is even more pronounced in the bis(dithioketal) **2**, where $H_{16}$ appears




at 6.65 ppm ($J$ = 1.7 Hz). Here the strong shielding effect exerted on the internal protons by the aromatic ring current is virtually neutralized by the deshielding of the two axial S atoms closest to $H_{16}$. Such a deshielding is also observed in the absorption of $H_{12}$ and $H_{14}$ in **2** (8.1 ppm) and of $H_{12}$ in **3** (8.1 ppm). In **3** the aromatic proton $H_{12}$ coplanar with the equatorial S atom appears at 8.1 ppm. The subsequent step was the reductive removal of the dithioketal function in **3**. Treatment of **3** with Raney nickel directly produced a 1:1 mixture of the diastereomeric alcohols **8E**–**8A** separable by chromatography, in 87% yield. In order to maintain the carbonyl function during the reductive desulfurization, the ketal **4** was prepared which upon Raney nickel treatment gave access to the crystalline ketal **5**. Surprisingly, it was found difficult to remove the ketal protecting group. Prolonged treatment in refluxing dioxane–hydrochloric acid was necessary to produce modest yields of ketonic material and various unidentified products. The rate determining step in this hydrolysis, quite obviously, is the rehybridization at $C_1$; going from $sp^3$ to $sp^2$ markedly increases the strain of the molecule and brings the internal potons into even greater proximity. However, the dimethylketal **6**, a stable, crystalline compound, produced the desired ketone **7** in 89% overall yield (**3** → **7**). The structure of the low melting (mp 79°) ketone **7** was corroborated by its spectral data. The low carbonyl frequency in the ir spectrum (1700 $cm^{-1}$), presumably and in analogy to the corresponding *p*-cyclophane analog,[14,15] reflects expanded OCC bond angles rather

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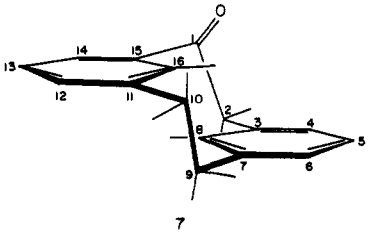
Table I. Nmr Data for 1-Oxo[2.2]metacyclophane and 1-Hydroxy[2.2]metacyclophane[a]

| Compd | $H_1$ a | $H_1$ e | $H_2$ a′ | $H_2$ e′ | $H_8$ | $H_{16}$ | $H_9$, a | $H_{10}$, e |
|---|---|---|---|---|---|---|---|---|
| 7 | | | 3.47 | 3.79 | 4.22 | 5.0 | 3.13 (m) | 2.05 (m) |
| | | | $J = 14$ | | | | | |
| 8E | 4.2 | | 2.16 | 3.29 | 4.25 | 4.17 | 3.07 (m) | 2.05 (m) |
| | $J_{aa'} = 10.5$ | | $J_{aa'} = 10.5$ | | | | | |
| | $J_{ae'} = 4.5$ | | $J_{a'e'} = 10.5$ | | | | | |
| | | | $J_{ae'} = 4.5$ | | | | | |
| 8A | | 5.18 | 2.34 | 3.19 | 4.60 | 4.26 | 3.10 | 2.07 |
| | | $J_{ee'} = 3.5$ | $J_{a'e} = 3$ | | | | | (apparent |
| | | $J_{a'e} = 3$ | $J_{a'e'} = 13$ | | | | | doublet) |
| | | | $J_{e'e} = 3.5$ | | | | | |

[a] The spectra were recorded in $CDCl_3$ solution on a Varian HR 220 spectrometer (we are indebted to Professor E. Wenkert for providing these spectra). Chemical shifts are expressed in ppm (δ) against TMS as internal standard. Coupling constants are given in Hz; a stands for axial, e for equatorial.

than conjugation. The lack of the acetophenone type chromophore in the uv spectrum confirms the nonplanarity of aromatic ring and carbonyl ($\measuredangle \approx 60°$). The nmr spectrum (see Table I) reveals the internal protons at δ 4.22 ($H_8$) and 5.0 ($H_{16}$) ppm (triplets) and the protons at $C_2$ as an AB spectrum. The protons at the unsubstituted ethane bridge are all nonequivalent and appear as an AA′BB′ type system.

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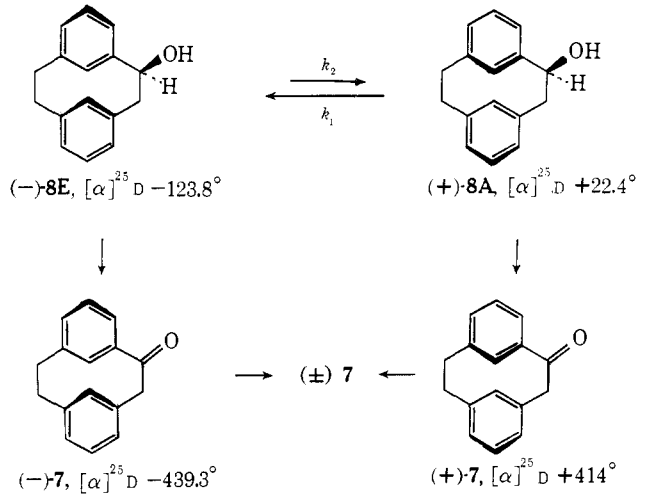
The ketone **7** was converted into a separable 1:1 mixture of isomeric oximes, the configurations of which were readily assigned on the basis of the marked differences in the nmr spectra. The syn oxime **9S** (syn arrangement of phenyl–OH) resembles the ketone **7** with the AB system at $\delta_A$ 3.83 and $\delta_B$ 3.09 ($J$ = 13 Hz). In the anti oxime **9A** in which the hydroxyl group and the equatorial $H_2$ are almost coplanar, the AB system transcends into an AX pattern with $\delta_A$ 4.98 and $\delta_X$ 2.69 ($J$ = 14 Hz).

Reduction of **7** with $Li(t\text{-}BuO)_3AlH$ in THF produced a 3:1 mixture of the equatorial and axial alcohols **8E** and **8A**, identical in all respects with those obtained by the Raney nickel procedure from **3**. The equatorial and axial configurational assignments again are based on the clearly different nmr spectra, the characteristics of which are tabulated in Table I.

**Resolution and Interconversion.** The resolution of the bridge-functionalized [2.2]metacyclophane skeleton was carried out on the equatorial alcohol **8E**. One diastereoisomer of the urethane, obtained by treating **8E** with (+)-α-phenylethyl isocyanate,[16] was isolated in pure form and subsequently reduced with $LiAlH_4$ to yield the optically active alcohol (−)-**8E**, $[\alpha]^{25}D$ −123.8° (*c* 1.39, $CHCl_3$), representing the metacyclophane analog to Cram's[17] 1-hydroxy[2.2]paracyclophane. Since (−)-**8E** contains two centers of chirality, namely, the inherent dissymmetry and the asymmetric carbinol carbon, oxidation to the corresponding ketone did not destroy the integrity of the molecular dissymmetry. Jones oxidation of (−)-**8E** proceeded only moderately well, probably because of an increase in strain during the rehybridization process, and produced the crystalline ketone (−)-**7** in *ca.* 50% yield. Another reason for the modest yield of (−)-**7** may be the oxidation of the internal hydrogens $H_8$ and $H_{16}$ leading to a tetrahydropyrene derivative. This kind of reaction has been observed before,[18] and it is possible that such products would be oxidized even further. Introduction of the carbonyl function into the ten-membered ring made the molecule highly asymmetric, as shown by its rather high specific rotation, $[\alpha]^{25}D$ −439.3° (*c* 1.19, $CHCl_3$), not uncommon in molecules with a pronounced inherent dissymmetry, such as helicenes[18,19] and biphenyls with restricted rotation.




In principle all the remaining isomers and enantiomers of the alcohols and the ketone, namely (+)-**8E**, (+)- and (−)-**8A**, and (+)-**7**, are accessible by processes involving oxidations, reductions, and thermal isomerizations, as demonstrated by the actual preparation of (+)-**8A** and (+)-**7**. By heating (−)-**8E** for 2 hr at 185°, conditions sufficient to reach the equilibrium as determined in the kinetic study, a 61:39 mixture of (−)-**8E** and a new axial alcohol was produced. While the process of the thermal inversion does not change the

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Table II. Kinetic Data for the Thermal Inversion of 1-Hydroxy[2.2]metacyclophane (8A/8E)

| Temp, °C ± 0.1 | Equilibrium constant $K$ | Rate constants $k_1 \times 10^4$, $sec^{-1}$ | Activation parameters $\Delta H^{\ddagger}$, kcal/mol | $\Delta S^{\ddagger}$, cal °K$^{-1}$ mol$^{-1}$ | $\Delta G^{\ddagger}_{150}$, kcal/mol |
|---|---|---|---|---|---|
| 146.1 | 1.4600 | 0.632 ± 0.015 | | | |
| 151.5 | 1.4907 | 1.191 ± 0.031 | | | |
| 154.0 | 1.5157 | 1.239 ± 0.049 | 31.7 ± 1.7 | −2.75 ± 4.0 | 32.9 |
| 156.8 | 1.5940 | 1.687 ± 0.062 | | | |
| 168.15 | 1.5478 | 4.099 ± 0.482 | | | |
| | | $k_2 \times 10^4$ | | | |
| 146.1 | | 0.433 ± 0.010 | | | |
| 151.5 | | 0.799 ± 0.021 | | | |
| 154.0 | | 0.818 ± 0.032 | 29.62 ± 1.7 | −8.5 ± 4.0 | 33.2 |
| 156.8 | | 1.059 ± 0.039 | | | |
| 167.15 | | 2.649 ± 0.311 | | | |

integrity of the chiral carbinol carbon, the inherent molecular dissymmetry of this axial alcohol must now be inverted and enantiomeric to the one of (−)-**8E**. Separation of this mixture yielded, besides recovered and unchanged (−)-**8E**, pure axial alcohol (+)-**8A** with a specific rotation of $[\alpha]^{25}D$ +22.4° (*c* 0.83, $CHCl_3$). The positive rotation suggests that in both alcohols the dominant contribution to the sign of rotation originates from the inherent dissymmetry of the skeleton, rather than the chiral carbon atom. Oxidation of (+)-**8A** again gave only a moderate yield of (+)-**7**. Besides the increase in strain, another factor recently described by Pople and Schleyer[20,21] might play an important role. As the intermediate chromic acid ester collapses to the ketone, a potential positive charge is developed at the carbinyl carbon. With the C–H and, subsequently, the empty $sp^3$ orbital forced, for geometrical reasons, into an almost orthogonal position to the $\pi$ system of the adjacent phenyl ring, the same destabilizing effect should come into play as the one observed in the rates of solvolysis of 2-methylene-1-adamantyl derivatives.[22] The ketone (+)-**7** was isolated and it exhibited a rotation of $[\alpha]^{25}D$ +414° (*c* 0.54, $CHCl_3$), thus only 5.7% below the maximal rotational value recorded for (−)-**7**.

**Kinetics of Ring Inversion. 1-Hydroxy[2.2]metacyclophane.** A 0.65–0.7 *M* solution of isomerically pure alcohol **8A** (or **8E**) in $C_6D_6$ was heated in a sealed nmr tube at temperatures above 140°. The rate of attainment of equilibrium was readily determined by comparing the integrations in the signal area of the

$$\mathbf{8A} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathbf{8E}$$

protons at $C_1$, $C_8$, and $C_{16}$ of the appearing **8E** at the expense of **8A** (or reversed). Data points (7–12) were collected until the equilibrium mixture was attained and the final concentrations (infinity point) were determined both by nmr spectroscopy and glc analysis of the silylated equilibrium mixture. Gas chromatography of the pure silylated alcohols did not produce any detectable inversions. The rates of equilibration were measured at four different temperatures (**8A**) and one additional temperature (154.0°) (**8E**). The data points and the equilibrium constant $k = k_1/k_2$ were analyzed by a simple linear regression computer program producing the rate constants $K_{obsd} = k_1 + k_2$ for this reversible first-order reaction.[23] The calculated standard deviation of the slope was used as the error for the rate constants. The activation parameters were calculated both from $k_1$ and $k_2$ at five different temperatures, using standard computer programs.[24] Table II records these data.

**1-Oxo[2.2]metacyclophane.** The rates of racemization of the ketone (−)-**7** were determined for three different temperatures. The reaction was followed by observing the change in the angular rotations ($\alpha_t$) at 589 and 365 nm on undiluted samples taken from a standard solution of (−)-**7** in decahydronaphthalene at 75.4 and 98.8° up to at least 70% of the reaction. The racemization at 25° was observed directly in a thermostated polarimeter cell (10-cm pathlength) by reading the angular rotation at 589, 436, and 365 nm over a period of 60 hr (60% racemization). The data points were analyzed by a simple linear regression computer program producing the observed racemization rate constants $2k$. According to the following equations[25] for this first-order racemization reaction, the reaction rate constants $k$ ($k = k'$) were used for the calculation

$$(-)\text{-}\mathbf{7} \underset{k'}{\overset{k}{\rightleftharpoons}} (+)\text{-}\mathbf{7}$$

$$k = \frac{1}{2t} \ln \alpha_0/\alpha_t$$

(standard computer program[24]) of the activation parameters. The calculated standard deviations of the slope were used as the limits of error for the rate constants. In the determination of the activation parameters, the limits of error include both the maximal deviation in the rate constants and temperature (least-squares method). These data as well as the half-lives ($t_{1/2}$) of the ketone (−)-**7** at the various temperatures are presented in Table III.

## Discussion

The kinetic parameters obtained by real time-scale measurements of the thermal ring inversion of 1-hydroxy[2.2]metacyclophane are, due to the modest sensitivities of the analytical methods (nmr integration, glc resolution), not as accurate as hoped for. The error of

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(21) L. Radom, J. A. Pople, V. Buss, and P. v. R. Schleyer, *ibid.*, **92**, 6380 (1970).
(22) V. Buss, R. Gleiter, and P. v. R. Schleyer, *ibid.*, **93**, 3927 (1971).
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Table III. Kinetic Data on the Thermal Racemization of (−)-1-Oxo[2.2]metacyclophane ((−)-7)

| Temp, °C ± 0.1 | $t_{1/2}$, hr | Racemization rate constants $2k \times 10^5$, $sec^{-1}$ | Activation parameters: $\Delta H^{\pm}$, kcal/mol | $\Delta S^{\pm}$, cal $°K^{-1}$ $mol^{-1}$ | $\Delta G^{\pm}_{25}$, kcal/mol |
|---|---|---|---|---|---|
| 98.8 | 1.26 | 15.3 ± 1.2 | | | |
| 75.4 | 1.78 | 10.8 ± 1.4 | 10.75 ± 0.19 | −48.4 ± 0.6 | 25.05 |
| 25.0 | 47.4 | 0.406 ± 0.015 | | | |

the $\Delta G^{\pm}$ values would appear to make the difference in the free energies of activation for the two reactions **8A** → **8E** and **8E** → **8A** insignificant and accidental. However, the trend in the equilibrium constant $K$ clearly indicates that the product ratio favors the equatorial alcohol **8E** at higher temperatures, suggesting that $\Delta\Delta S^{\pm}$ is at least qualitatively correct. The measured $\Delta G^{\pm}$ values of *ca.* 33 kcal/mol clearly support the qualitative estimates[5b,8] for $\Delta G^{\pm}$ of [2.2]metacyclophane (**1**) itself being higher than 27 kcal/mol. The value of 33 kcal/mol may even seem a rather low-energy barrier. Two questions clearly arise: first, are the alcohols **8E** and **8A** an adequate model for the ring inversion of unsubstituted **1**, and second, are we dealing with a real ring inversion? Although minor substituent effects on the free energies of activation were observed in the inversion studies of [3.2]metacyclophane,[8] the OH group in **8A** or **8E** would not appear to drastically change the gross steric nature of the [2.2]metacyclophane skeleton. However, a carbon–carbon bond dissociation, which is the predominant pathway in the isomerization (racemization) of [2.2]paracyclophanes,[2,26] cannot be excluded. In particular the alcohol function would even enhance the possibility of such a process and furthermore most of the benzylic character of the ethano bridge carbons is located in the $\sigma$ bond between $C_1$–$C_2$ and $C_9$–$C_{10}$, *i.e.* the $\sigma$ bonds are nearly in an orthogonal position to the $\pi$ system of the aromatic nuclei. These circumstances are also the reason behind the inertness of the bridge hydrogens toward reagents which would otherwise oxidize normal benzylic positions.[1] Since the corresponding $\sigma$ bond in [2.2]paracyclophane is similarly overlapping with the $\pi$ system and since the free energy of activation for the bond breaking process, leading to the observed racemization of the 4-carbomethoxy derivative, has been determined to be approximately 38 kcal/mol,[26] the observed $\Delta G^{\pm}$ of 33 kcal/mol in the case of 1-hydroxy[2.2]metacyclophane is only 5 kcal/mol below the energy needed to effect the bond breaking process.

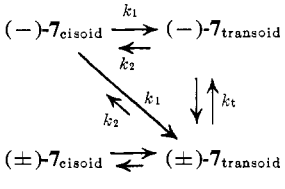
Three facts, however, were gathered which suggest that ring inversion in the alcohols **8E**/**8A** is real and does not proceed *via* a diradical. First, a CIDNP experiment at 160–180°, following the methods described,[27–29] did not disclose the intermediacy of a diradical.[30] While this is a negative proof and since signal emissions of this type are only rarely observed in true diradicals[31] a trapping experiment was carried out in analogy to the ones reported by Cram[26] for [2.2]paracyclophane. When **8E** was heated in an excess of dimethyl maleate at 180° for 2 hr, conditions sufficient to produce the equilibrium, no adduct (such as the one described by Cram[26]) was observed and **8E** was recovered unchanged. The third piece of evidence for the true inversion process was maintenance of the stereochemical integrity of the carbinol carbon $C_1$, whose configuration was retained in the process described for the transformation of (−)-**8E** ⇄ (+)-**8A** → (+)-**7**. The intermediacy of a diradical would almost certainly produce a loss in optical activity. These three facts indicate that the [2.2]metacyclophane skeleton inverts, unlike the [2.2]paracyclophane, *via* a true ring inversion. It is now also evident that the $H_8$ to $H_{16}$ nonbonded interaction in the transition state for **8E** ⇆ **8A** does not prevent ring rotation in the [2.2]metacyclophane skeleton at attainable temperatures.

While molecular models suggest that the inversion process in 1-oxo[2.2]metacyclophane may be somewhat more facile, the steric and geometric features are rather similar to those in the alcohols. In view of such obviously superficial similarities, the vast change in the values of the kinetic parameters was rather unexpected. The very broad temperature range within which the rates of racemization could conveniently be measured was the first qualitative sign of a large, negative entropy term. The opportunity to measure rate constants at temperatures so far apart results in a fairly accurate slope of the Arrhenius plot and thus reliable kinetic parameters. Whereas the entropy term contributing to the free energy of activation of ~33 kcal/mol for the alcohols **8A** → **8E** is almost negligible, $\Delta S^{\pm}$ is the major factor in the $\Delta G^{\pm}$ value for the inversion of the ketone (−)-**7**. Although observations of rather large negative $\Delta S^{\pm}$ values in the thermal racemization of sterically hindered compounds have been made,[25,32] a value of $\Delta S^{\pm} = -48.4$ cal $°K^{-1}$ $mol^{-1}$ for (−)-**7** seems without precedent. Questions about the stability of **7** as well as the mechanism and even the geometry of the transition state of the inversion clearly arise. The stability of (±)-**7** was demonstrated by observing an unchanged nmr spectrum (in *o*-$Cl_2C_6H_4$) from 25 to 150°. By analogy with the alcohols the following trapping experiments tend to exclude the intermediacy of a ring opened form, such as a zwitterion, or a diradical. Heating of (±)-**7** at 110° for 4 hr in methanol or for 3 hr in dimethyl maleate has led only to a recovery of the ketone (±)-**7** and did not yield any detectable amounts of trapping products. The cause for the high $\Delta S^{\pm}$ value, or conversely, for the low enthalpy of activation, must be related to the carbonyl function. As proposed earlier by Eyring[25] for hindered diphenyls, $\Delta H^{\pm}$ for (−)-**7** could similarly be

(26) H. J. Reich and D. J. Cram, *J. Amer. Chem. Soc.*, **91**, 3517 (1969).
(27) H. Fischer and J. Bargon, *Accounts Chem. Res.*, **2**, 110 (1969).
(28) S. H. Tine, *J. Chem. Educ.*, **48**, 101 (1971).
(29) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **91**, 4549 (1969).
(30) The careful execution of these experiments by Dr. J. Karliner is acknowledged.
(31) G. L. Closs, *J. Amer. Chem. Soc.*, **93**, 1546 (1971), and references cited therein.
(32) D. M. Hall and M. M. Harris, *J. Chem. Soc.*, 490 (1960).

broken down as a first approximation into two terms: one, called $b$, representing the energy necessary to distort the bonds in such a way that coplanarity of phenyl with carbonyl can be brought about; the other term $a$, reflecting the resonance energy that results from such a conformation. For the ketone **7** one would then write $\Delta H^{\pm} = b - a = 10.75$ kcal/mol. In qualitatively comparing the $\Delta H^{\pm}$ values of **8A** → **8E** with the one for (−)-**7** the latter would be smaller by the increment $a$, reflecting the resonance energy. The same difference of $a$ should also be found in the $\Delta G^{\pm}$ values, *i.e.*, the free energy of activation for the ring inversion of (−)-**7** should be, as a first approximation, lower by the amount of resonance energy between phenyl and carbonyl. Such a hypothesis finds some support in the fact that the difference in $\Delta G^{\pm}_{25}$ for **8A** → **8E** and $\Delta G^{\pm}_{25}$ for (−)-**7** of 7.1–7.5 kcal/mol is very close to the empirical resonance energy of 7 kcal/mol determined for acetophenone.[33] By extrapolating the more recent kinetic data[34,35] of the nmr spectroscopically determined energy barriers ($\Delta G^{\pm}$) for the C–C bond rotation in substituted acetophenones and benzaldehydes to acetophenone itself, a $\Delta G^{\pm}_{25}$ of 6–8 kcal/mol is obtained, a value which is conspicuously close to our $\Delta\Delta G^{\pm}$ of 7.1–7.5 kcal/mol. In the ring inversion of the ketone **7** then, whose ground state is inherently strained, the requisite coplanarity of carbonyl and adjacent phenyl moieties in the transition state all but eliminates the remaining degrees of freedom. Thus, the −48 cal °K$^{-1}$ mol$^{-1}$ observed for the entropy of activation in the inversion of 1-oxo[2.2]metacyclophane is at least consistent with the view that ring inversion occurs *via* a transition state that is extraordinarily rigid and therefore highly improbable.

On the basis of the present data, however, other explanations for the unusual $\Delta S^{\pm}$ value cannot be discounted. Thus, the inversion of (−)-**7** may follow two or more paths with different kinetic parameters and, if so, the simple first-order one-mechanism treatment of the measured rates results in unusual enthalpies and entropies of activation. An alternative possibility[36] for the ketone (−)-**7** would be a one-sided equilibrium between the "transoid" and a minute population of the "cisoid" conformers, resulting in a considerably more complex reaction. Evidently, a hypothetical situation




$$k_1 \gg k_2$$

in which $k_2$ and $k_t$ are of the same order of magnitude would call for a different kinetic treatment of the observed rates of racemization.

The ORD and CD curves of (−)-1-oxo[2.2]metacyclophane and the prediction of its absolute configuration shall be reported later.

## Experimental Section

**General.** Melting points are uncorrected and were taken in a Thomas-Hoover melting point apparatus. Nmr spectra were recorded on a Varian A-60 instrument unless otherwise specified. Optical rotations were determined with a Perkin-Elmer 141 polarimeter and a 1-dm thermostated cell in chloroform. In description of nmr data, s = singlet, d = doublet, t = triplet, m = multiplet, and the numbers that follow these letters indicate the number of protons the signal represents.

**Dithioketal 2.**[8] *m*-Phthalaldehydedithioketal (12.56 g; 40 mmol) was dissolved in 700 ml of freshly distilled tetrahydrofuran (over NaH) and cooled to −30° under a positive $N_2$ pressure. *n*-Butyllithium (50 ml; 1.6 *M*) in hexane was added with stirring over a period of 25 min. The reddish dianion was stirred for an additional 30 min at −20 to −30°. This solution was transferred into a graduated dropping funnel under rigorous exclusion of moisture and oxygen. In a second dropping funnel a solution of 10.56 g of *m*-xylylene dibromide (40 mmol) in 200 ml of dry THF was prepared. Both dropping funnels were placed on a three-necked 2-l. flask containing 500 ml of THF and equipped with a magnetical stirrer and a $N_2$ inlet. Then both reagents were added to the vigorously stirred THF over a period of 1.5–1.75 hr at a proportional rate. After the addition the reaction mixture was stirred for 3 more hr at room temperature. The THF was then removed *in vacuo*. The residue was taken up in benzene and thoroughly washed with water. The aqueous layers were extracted with three portions of benzene. After drying over $Na_2SO_4$ and removal of the solvent *in vacuo*, the residue was crystallized from benzene. A first crop usually yields 9–10.5 g (mp 238–240°) and a second crop between 0.7 and 1.1 g (mp 237–240°). The yields in ten separate runs described above varied between 64 and 71%, before chromatography, depending upon rate of addition of reagents. The product usually (but not consistently) crystallized with 0.5 mol of benzene which was lost when heated above 160°: nmr ($CDCl_3$) δ 1.6–3.4 (m, 12 H), 2.45 and 3.28 (AB, $J_{AB}$ = 12 Hz, 4 H), 4.0 (br, 1 H), 6.65 (three lines, $J$ = 1.7 Hz, 1 H), 7.15–7.7 (m, 6 H), 8–8.2 (m, 2 H).

*Anal.* Calcd for $C_{22}H_{24}S_4$ ($+0.5C_6H_6$): C, 63.40 (65.99); H, 5.80 (5.98). Found: C, 65.65; H, 5.87.

**Selective Deketalization 2 → 3.** Dithioketal **2** (10 g, 24 mmol) was dissolved in 800 ml of dioxane (distilled over Na) which was warmed to 90°. To this solution was added a solution of 32 g of $HgCl_2$ in 400 ml of water (85° warm) and the reaction mixture was then refluxed under $N_2$ for 16 hr. After cooling to room temperature, the mixture was filtered and the filtrate concentrated *in vacuo*.

The filter residue was thoroughly washed with $CH_2Cl_2$ which then was used to take up the residue of the filtrate concentrate. The organic layer was washed twice with 10% $NH_4Cl$ solution and subsequently dried over $Na_2SO_4$. After removal of the solvent the residue was combined with those of three other identical runs. The 30-g residue was dissolved in 300 ml of hot benzene. Upon cooling, 9.13 g of the monoketone **3** was collected (mp 212–215°). Recrystallization from $CH_2Cl_2$–ether gave 8.70 g (mp 215–217°) and 0.65 g (mp 214–217°). The combined mother liquors were chromatographed on 370 g of neutral $Al_2O_3$ (I). Elution with benzene (six fractions) gave 10.37 g (after recrystallization from $CH_2Cl_2$–ether) of starting material (26%). Benzene–ethyl acetate (4:1) yielded the product: 4.5 g; mp 212–215°; yield 42%. An analytical sample (mp 215–217°) showed the following characteristics: ir (Nujol) 1700 cm$^{-1}$; uv ($CH_3OH$) 262 mμ (ε 1050); nmr ($CDCl_3$) δ 1.7–3.2 (m, 6 H), 2.48 (d, $J_{AB}$ = 13 Hz, 1 H), 3.4–3.92 (four lines, $J_{AB}$ = 14 Hz, 2 H), 4.9 (s, 1 H), 5.6 (m, $J \sim 1$ Hz, 1 H), 7.1–7.65 (m, 5 H), 8–8.25 (six lines, $J$ = 1.5 and 7.5 Hz, 1 H), 3.43 (d, $J_{AB}$ = 13 Hz, 1 H).

*Anal.* Calcd for $C_{19}H_{18}OS_2$: C, 69.89; H, 5.56. Found: C, 70.16; H, 5.73.

**Ethylene Ketal 4.** A solution of 750 mg (2.3 mmol) of ketone **3** was refluxed in 50 ml of benzene with 0.75 ml of ethylene glycol and 50 mg of *p*-toluenesulfonic acid under a water separator for 17.5 hr. Upon cooling, the reaction mixture was diluted with $CH_2Cl_2$ and washed with aqueous $Na_2CO_3$. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. The residue was crystallized

(33) L. Pauling and J. Sherman, *J. Chem. Phys.*, **1**, 606 (1933). The value of 7 kcal/mol, however, is in sharp contrast to the virtually negligible gain in resonance energy for acetophenone (*vs.* ethylbenzene) reported by F. Klages, *Chem. Ber.*, **82**, 358 (1949).

(34) F. A. L. Anet and M. Ahmad, *J. Amer. Chem. Soc.*, **86**, 119 (1964).

(35) R. E. Klinck, D. H. Marr, and J. Stothers, *Chem. Commun.*, 409 (1967).

(36) The possibility of a relatively small energy difference between the "transoid" and "cisoid" forms of **7** and its complicating implications for the measurement and calculation of the kinetic parameters has kindly been suggested by Professor N. L. Allinger, one of the referees of this paper.

from ether to yield 690 mg of ketal: mp 165°; nmr ($CDCl_3$) $\delta$ 1.2–3.7 (m, 14 H), 3.7 (s, 1 H), 5.33 (s, 1 H), 6.7 (s, 3 H), 7.0 (m, 2 H), 7.5 (m, 1 H).

*Anal.* Calcd for $C_{21}H_{22}O_2S_2$: C, 68.09; H, 5.99. Found: C, 67.79; H, 6.08.

**Desulfurization 4 → 5.** Ketal **4** (400 mg) was refluxed with 16 ml of Raney nickel (washed five times with water, ten times with ethanol) suspended in 35 ml of ethanol for 6 hr. After filtration, the ethanol was removed *in vacuo* to yield a crystalline residue of 220 mg (mp 137°). Recrystallization of this material from ether gave 80 mg: mp 143°; nmr ($CDCl_3$) $\delta$ 1.8–2.3 (m, 2 H), 2.5–3.2 (four lines, $J_{AB}$ = 13 Hz, 2 H), 2.7–3.3 (m, 2 H), 3.5–4.3 (m, 4 H), 4.3 (s, 1 H), 4.66 (s, 1 H), 6.9–7.5 (m, 6 H)

**Dimethyl Acetal 3 → 6.** The monoketone **3** (5.0 g, 15.3 mmol) was refluxed for 6 hr in 250 ml of dry methanol, containing 2 ml of 2.8 *N* ethereal HCl. Upon cooling, the dimethyl ketal **6** crystallized. It was filtered (mp 155°) and the filtrate evaporated to dryness: ir (Nujol) 1100, 1070, 1020 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.7–3.3 (m, 10 H), 3.24 (s, 3 H), 3.52 (s, 3 H), 4.1 (m, br, 1 H), 5.98 (m, br, 1 H), 7.2–7.7 (m, 5 H), 7.95–8.25 (m, 1 H).

*Anal.* Calcd for $C_{21}H_{24}O_2S_2$: C, 67.77; H, 6.50. Found: C, 67.97; H, 6.59.

**Desulfurization 6 → 7.** The crude product from the above reaction (5.7 g, including filtered product and solid obtained after evaporation of the filtrate) was refluxed for 6 hr in 250 ml of ethanol and "100 ml" of Raney nickel (= 100 ml of sedimented suspension in ethanol, previously washed ten times with distilled water and ten times with ethanol). The mixture was then filtered and the solvent evaporated *in vacuo* to give 3.4 g (100% overall) of crystalline ketone **7**, mp 71–76°. Recrystallization from hexane gave 2.57 g of a first crop (mp 79–81°) and 450 mg of a second crop (mp 76–79°) (89%). The analytical data were obtained on a sample melting at 79–81°: ir (Nujol) 1700, ($CH_2Cl_2$) 1700 $cm^{-1}$; uv ($CH_3OH$) 273 m$\mu$ ($\epsilon$ 555); nmr ($CDCl_3$) $\delta$ 1.7–2.4 (m, 2 H), 2.8–3.3 (m, 2 H), 3.42 and 3.8 ($J_{AB}$ = 14 Hz, 2 H), 4.22 (t, $J \sim 1$ Hz, 1 H), 5.0 (t, $J \sim 1$ Hz, 1 H), 6.9–7.5 (m, 6 H).

*Anal.* Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.15; H, 6.25.

**Preparation of 1-Hydroxy[2.2]metacyclophanes 8E and 8A.**

**(a) Directly from 3.** The monoketone **3** (1.0 g, 3.06 mmol) was dissolved in 120 ml of ethanol and refluxed for 6 hr with 20 ml of an ethanolic suspension of pyrophoric Raney nickel. After filtration and removal of the solvent the residue was taken up in ether, filtered through Celite, and again evaporated. The residue (700 mg) was separated by preparative thick layer chromatography (silica–$CHCl_3$) to give the solid alcohols in about equal amounts (crude yield after separation, 87%): $R_f$ 0.3 (289 mg) and 0.45 (308 mg). Both epimers were recrystallized from hexane.

Axial alcohol **8A**: $R_f$ 0.45; 240 mg; mp 133–134°; ir ($CH_2Cl_2$) 3602 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.85 (s, exch, 1 H), 1.9–2.5 (m, 3 H), 2.8–3.3 (m, 3 H), 4.26 (s, br, 1 H), 4.60 (s, br, 1 H), 5.18 (t, $J$ = 3 Hz, 1 H), 6.8–7.5 (m, 6 H).

*Anal.* Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 86.00; H, 7.18.

Equatorial alcohol **8E**: $R_f$ 0.3; 220 mg; mp 136–137°; ir ($CH_2Cl_2$) 3606 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.8–2.4 (m, 3 H), 2.75 (s, exch, 1 H), 2.7–4.4 (m, 3 H), 4.17 (s, br, 1 H), 4.25 (s, br, 1 H), 4.1–4.35 (m, 1 H), 6.9–7.5 (m, 6 H).

*Anal.* Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.75; H, 7.27.

**(b) From Ketone 7.** Ketone **7** (1.8 g, 8.1 mmol) was dissolved in 120 ml of dry THF and stirred for 22 hr with 4.1 g (16.2 mmol) of Li(*t*-BuO)$_3$AlH under $N_2$. Upon cooling and dilution with ether excess reagent was destroyed with dilute HCl and the organic layer separated. After a second extraction the ethereal layers were washed with brine, dried over $Na_2SO_4$, and evaporated to give 1.8 g of solid product. From AcOEt–hexane a first crop of 890 mg of **8E** (mp 135–137°) and a second crop (130 mg) of **8E** (mp 132–135°) were obtained. The mother liquor was a 56:44 mixture (by nmr) of essentially pure **8A** and **8E**; thus an analytical yield of 75% equatorial (**8E**) and 25% axial (**8A**) alcohols was obtained. Larger scale preparations of the mixture of alcohols were effectively separated by column chromatography, *e.g.*, 2.55-g mixture (prepared as described under a) chromatographed on 80 g of silica (Merck, 0.05–0.2 mm) using $CH_2Cl_2$ as eluent; fractions 10–19 contained exclusively **8A**, 20–21 were mixed (10%), and 22–27 were clean **8E**.

**Oximation 7 → 9S + 9A.** Ketone **7** (300 mg, 1.35 mmol) was stirred in 4.2 ml of dry pyridine with 300 mg of $NH_2OH \cdot HCl$ at 40° for 18.5 hr. The pyridine was removed *in vacuo*, and the residue taken up in ethyl acetate, washed with cold 0.5 *N* HCl, and dried over $Na_2SO_4$. After evaporation of the solvent *in vacuo* the components were separated by thick layer chromatography (silica gel GF, cyclohexane-*i*-PrOH (9:1)).

Isomer **9A** ($R_f$ 0.7), 122 mg, recrystallized from ether–hexane to give 70 mg: mp 147°; nmr ($CDCl_3$) $\delta$ 1.8–2.4 (m, 2 H), 2.8–3.4 (m, 2 H), 2.7 (d, $J_{AX}$ = 14 Hz, 1 H), 4.88 (d, $J_{AX}$ = 14 Hz, 1 H), 4.33 (s, 1 H), 4.77 (s, 1 H), 7.0–7.5 (m, 6 H), 9.6 (br, 1 H).

Isomer **9S** ($R_f$ 0.6), 124 mg, recrystallized from ether–hexane to give 70 mg: mp 157°; nmr ($CDCl_3$) $\delta$ 1.8–2.4 (m, 2 H), 2.8–3.4 (m, 2 H), 2.95–3.95 (four lines, $J_{AB}$ = 13 Hz, 2 H), 4.23 (s, 1 H), 4.7 (s, 1 H), 7.0–7.5 (m, 6 H), 9.1 (s, 1 H).

*Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.62; H, 6.17; N, 5.79.

**Resolution of 1-Hydroxy[2.2]metacyclophane 8E → (−)-8E.** The alcohol **8E** (1.5 g, 6.7 mmol) was stirred at 80° under $N_2$ in 12 ml of dry THF and 2 g of (+)-1-phenylethyl isocyanate[16] for 36 hr. The solvent was then removed *in vacuo* and the solid residue filtered through 50 g of silica (Merck, 0.05–0.2 mm) with $CH_2Cl_2$ as solvent. In five fractions (120 ml each) 2.4 g of adduct (diastereomeric mixture) was obtained which was pure by tlc (silica gel GF, $R_f$ 0.85 ($CHCl_3$)). Crystallization from ether gave three fractions: (1) mp 178–181° (800 mg); (2) mp 128–132° (850 mg); (3) mp 129–132° (400 mg). Recrystallization of fraction 1 produced 750 mg, mp 181–182°. Two subsequent recrystallizations from AcOEt–hexane did not raise the mp: $[\alpha]^{26}D$ −151.8° (*c* 1.34, $CHCl_3$).

The urethane (300 mg) was dissolved in 75 ml of dry ether under $N_2$ and stirred with 300 mg of $LiAlH_4$ for 10 hr. Excess hydride was destroyed with water, the aqueous phase acidified with 2 *N* HCl, and the product extracted with ether. After washing the solution with brine, drying over $Na_2SO_4$, and removal of the solvent *in vacuo*, 180 mg of solid alcohol was obtained (>95%), essentially pure by tlc. The alcohol was recrystallized from a trace of $CH_2Cl_2$–ether to give 98 mg of fluffy crystals, mp 152–153°, $[\alpha]^{25}D$ −123.8° (*c* 1.39, $CHCl_3$).

**Oxidation (−)-8E → (−)-7E.** After a trial experiment on racemic alcohol **8E** the following conditions were used. Alcohol (−)-**8E** (90 mg) was dissolved in 7 ml of acetone and stirred at room temperature with 0.5 ml of Jones reagent[37] for 2.5 hr. The acetone was removed *in vacuo* and the residue taken up in water and $CH_2Cl_2$ and washed with $NaHSO_3$. After drying the organic layer over $Na_2SO_4$ and removal of the solvent, a residue of 50 mg was obtained. This material was filtered through a short column of silica, using benzene as solvent. The first three fractions (20 ml) contained 45 mg of crystalline ketone (−)-**7**. Recrystallization from hexane at −20° produced two large crystals, mp 110.5–111° (28 mg): $[\alpha]^{25}D$ −439.3° (*c* 1.19, $CHCl_3$); 589 nm, −439.3°; 578 nm, −466.0°; 546 nm, −555.4°; 436 nm, −1311.3°.

**Thermal Equilibration (−)-8E ⇄ (+)-8A.** Alcohol (−)-**8E** (145 mg of crude product obtained from the $LiAlH_4$ reduction of the pure urethane) was dissolved in 4 ml of benzene and heated in a sealed tube at 185° for 2 hr. The tube was opened, the solvent evaporated, and the solid residue separated on a 20 × 20 cm silica plate (1000 $\mu$, GF, Analtech). The front of the main band (36 mg) was pure axial alcohol (+)-**8A** (nmr, tlc). The lower part of the main fraction (54 mg) was pure (tlc) equatorial alcohol (−)-**8E** and the middle part of the main fraction (28 mg) consisted of a mixture of the two alcohols (tlc). The 36 mg of (+)-**8A** was recrystallized from ether to give 12.5 mg: mp 137–138°; $[\alpha]^{25}D$ +22.4° (*c* 0.83, $CHCl_3$).

**Oxidation (+)-8A → (+)-7.** After a trial experiment on racemic alcohol **8A**, the following conditions were employed. Axial alcohol (+)-**8A** (35 mg) was dissolved in 5 ml of acetone and stirred at room temperature for 3 hr with 0.24 ml of Jones reagent. The work-up procedure was then as described for (−)-**7**. The residue of 23 mg was separated on a 20 × 20 silica plate (1000 $\mu$, GF, Analtech), using benzene as eluent. The weakly fluorescent fraction contained 18 mg (55%) of solid ketone which was recrystallized from pentane at −20° to give four crystals (7 mg): mp 102–103°; $[\alpha]^{25}D$ +414.0° (*c* 0.54, $CHCl_3$).

**Trapping Experiment. 8E + Dimethyl Maleate.** Alcohol **8E** (60 mg) was heated in a sealed tube in 0.4 ml of freshly distilled dimethyl maleate at 180° for 2 hr. The tube was then opened and the diester distilled at 75° (0.4 mm). The crystalline residue of 60 mg was dissolved in $CDCl_3$ and the nmr spectrum recorded. The spectrum revealed the familiar equilibrium mixture of **8E**:**8A** = 61:39 and no trace of a dimethyl maleate adduct.

(37) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 21, 1547 (1956).

**CIDNP. Experiment with 8E.** A 10% solution of **8E** in *o*-dichlorobenzene was raised gradually from 30 to 185° in the nmr probe. Although conversion of the originally pure **8E** into the 61:39 equilibrium mixture was noticed (**8E**:**8A**) no CIDNP effects (emissions) were detected.

A mass spectrum of this mixture taken between 80 and 250° did not provide any peaks which could be ascribed to a dimer of 1-hydroxy[2.2]metacyclophane.

**Trapping Experiments. (a) 7 + Dimethyl Maleate.** A solution of 35 mg of **7** in 0.25 ml of distilled dimethyl maleate was heated under an atmosphere of $N_2$ at 110° for 3 hr. Dimethyl maleate was then distilled at 80° (0.1 mm). An nmr spectrum of the crystalline residue as well as a tlc (silica gel–benzene, $R_f$ 0.44) showed it to be unchanged **7**.

**(b) 7 + $CH_3OH$.** A solution of 35 mg of **7** in 0.5 ml of absolute $CH_3OH$ was heated in a sealed tube in an oil bath at 110° for 4 hr. The tube was then opened and the $CH_3OH$ distilled. An nmr spectrum of the crystalline residue revealed no trace of any $CH_3O$ signals and was identical with pure **7**.

**Rate of Racemization of (−)-7.** In a typical run 11 mg of ketone (−)-**7** was dissolved in 13 ml of spectrograde decahydronaphthalene in a 1-cm diameter tube which was immersed in a constant temperature silicone oil bath. The temperatures recorded inside the tube were constant to ±0.1° during the two runs. At 1-hr intervals a 1-ml sample of this solution was removed and chilled in an ice bath. The angular rotations on such a sample were then recorded at 25° without any further dilution. The time–temperature lag resulting from the point of immersion to the attainment of the final temperature was automatically corrected by the computer analysis of the plot log $\alpha_0/\alpha_t$ *vs.* time (Table IV).

**Table IV**

| Time, min | $\alpha_t$ at 589 mm | $\alpha_t$ at 365 mm |
|---|---|---|
| | 98.8° | |
| 0 | 0.218 | 2.153 |
| 60 | 0.142 | 1.451 |
| 120 | 0.085 | 0.853 |
| 180 | 0.051 | 0.571 |
| 240 | 0.026 | 0.276 |
| | 75.4° | |
| 0 | 0.353 | 3.860 |
| 60 | 0.310 | 3.424 |
| 120 | 0.234 | 2.241 |
| 180 | 0.157 | 1.558 |
| 240 | 0.102 | 1.001 |

All eight values of $\alpha_0/\alpha_t$ were used for the linear regression computer analysis to produce the observed racemization rate constants $2k$.

The measurements at 25.0° were directly carried out on a solution of (−)-**7** in decahydronaphthalene in a thermostated (10-cm pathlength) polarimeter cell. The angular rotations $\alpha_t$ were observed at 589, 436, and 365 nm over a period of 60 hr (see Table V). All 22 values of $\alpha_0/\alpha_t$ were used for the linear regression analysis of $2k$.

**Rates of Inversion of 8E/8A.** In a typical run a 0.65–0.7 *M* solution of isomerically pure **8A** (or **8E**) in $C_6D_6$ was sealed in an nmr tube and fully immersed in a constant temperature silicone oil bath (±0.1°). At given time intervals the tube was removed from the bath and chilled in an ice bath and the spectrum recorded at 30°, in particular the signal area of protons at $C_1$, $C_8$, and $C_{16}$. The protons at $C_1$ and $C_{16}$ of the axial alcohol were sufficiently isolated to allow for the determination of the ratio axial:equatorial. This area was integrated six times and the mean values ($C_A$) were used. The final concentrations ($C_{A_e}$) were determined by glc analysis of the silylated equilibrium mixture (support Chromgas 60/70, coating sp 400, column temperature, 180°) (Table VI). The mean average of three determinations was used. By plotting log $(C_{A_0} - C_{A_e}/C_A - C_{A_e})$ *vs.* time straight lines were obtained.

**Table V**

| Time, hr | $\alpha_t$ at 589 nm | $\alpha_t$ at 436 nm | $\alpha_t$ at 365 nm |
|---|---|---|---|
| | 25° | | |
| 0 | 0.445 | 1.288 | 4.604 |
| 6 | | 1.228 | 4.405 |
| 8 | | 1.200 | 4.301 |
| 24 | 0.321 | 0.886 | 3.052 |
| 25 | 0.315 | 0.872 | 3.004 |
| 35 | 0.282 | 0.759 | 2.604 |
| 35.5 | 0.263 | 0.751 | 2.580 |
| 49.5 | 0.234 | 0.626 | 2.182 |
| 60 | 0.192 | 0.552 | 1.984 |

**Table VI**

| Time, min | $C_A$, *M* | $(C_{A_0} - C_{A_e}/C_A - C_{A_e})$ |
|---|---|---|
| | 167.15°, **8A**, $C_{A_0}$ = 1.0, $C_{A_e}$ = 0.3925 | |
| 15 | 0.7394 | 1.751 |
| 30 | 0.5948 | 3.003 |
| 45 | 0.4760 | 7.275 |
| 60 | 0.4384 | 13.235 |
| 75 | 0.4307 | 15.903 |
| 120 | 0.4039 | 53.289 |
| 135 | 0.3938 | 467.310 |
| | 156.8°, **8A**, $C_{A_0}$ = 1.0, $C_{A_e}$ = 0.3855 | |
| 15 | 0.8741 | 1.257 |
| 30 | 0.7875 | 1.528 |
| 45 | 0.7041 | 1.929 |
| 60 | 0.6279 | 2.535 |
| 75 | 0.5520 | 3.691 |
| 90 | 0.5338 | 4.144 |
| 105 | 0.5037 | 5.199 |
| 120 | 0.4656 | 7.672 |
| 135 | 0.4602 | 8.226 |
| | 154.0°, **8E**, $C_{A_0}$ = 0.0, $C_{A_e}$ = 0.3975 | |
| 15 | 0.0428 | 1.121 |
| 30 | 0.1372 | 1.527 |
| 45 | 0.1828 | 1.851 |
| 60 | 0.2146 | 2.173 |
| 75 | 0.2484 | 2.666 |
| 90 | 0.2829 | 3.469 |
| 105 | 0.2961 | 3.920 |
| 120 | 0.3215 | 5.230 |
| 135 | 0.3206 | 5.169 |
| 150 | 0.3358 | 6.443 |
| 180 | 0.3621 | 11.229 |
| 210 | 0.3638 | 11.795 |
| | 151.5°, **8A**, $C_{A_0}$ = 1.0, $C_{A_e}$ = 0.4015 | |
| 15 | 0.9640 | 1.064 |
| 30 | 0.8405 | 1.363 |
| 45 | 0.7506 | 1.714 |
| 60 | 0.7111 | 1.933 |
| 75 | 0.6560 | 2.352 |
| 90 | 0.6126 | 2.835 |
| 105 | 0.5759 | 3.432 |
| 120 | 0.5531 | 3.948 |
| 135 | 0.5112 | 5.456 |
| | 146.1°, **8A**, $C_{A_0}$ = 1.0, $C_{A_e}$ = 0.4065 | |
| 15 | 0.9623 | 1.068 |
| 30 | 0.8978 | 1.208 |
| 45 | 0.8555 | 1.322 |
| 60 | 0.8120 | 1.464 |
| 75 | 0.7694 | 1.635 |
| 90 | 0.7264 | 1.855 |
| 105 | 0.7100 | 1.956 |
| 120 | 0.6707 | 2.246 |
| 150 | 0.6269 | 2.693 |
| 240 | 0.5261 | 4.462 |

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