by ^{1}H NMR or analytical GC. The melting point of the mixture showed softening at ca. 50 °C with complete melting at 110 °C. The anti isomer **2** was completely separated from the syn isomer **1** by slow and repeated fractional sublimation at atmospheric pressure at 55 °C or by preparative GC. Thus, the more volatile syn isomer **1** was removed by sublimation to leave the less volatile anti isomer **2** behind as a white solid, mp 118-121 °C (racemate mp 120-122 °C), after crystallization from methanol-water. Ketone **2** had the following: $[\alpha]^{25}_{589}$ 0°, $[\alpha]^{25}_{578}$ 0°, $[\alpha]^{25}_{436}$ +23.92°, $[\alpha]^{25}_{365}$ +55.55° (*c* 0.35); UV (MI) ϵ^{max}_{300} = 21; UV (EPA ϵ^{max}_{299} = 29; CD (isopentane) $\Delta\epsilon^{max}_{314}$ = -0.07, ϵ^{max}_{188} = +3.4; CD (MI) $\Delta\epsilon_{270}$ = 0, $\Delta\epsilon_{306}$ = -0.034, $\Delta\epsilon_{320}$ = -0.056, $\Delta\epsilon_{332}$ = -0.046, $\Delta\epsilon_{339}$ = 0; CD (EPA) $\Delta\epsilon_{262}$ = 0, $\Delta\epsilon_{302}$ = +0.045, $\Delta\epsilon_{312}$ = +0.040, $\Delta\epsilon_{324}$ = +0.007, $\Delta\epsilon_{327}$ = 0, $\Delta\epsilon_{332}$ = -0.023, $\Delta\epsilon_{338}$ = 0 (CD run at room temperature); IR (CCl_4) ν 1770 cm^{-1}; ^{1}H NMR δ 1.07 (d, 2 H, J = 8 Hz, CH_3) and 2.72-3.12 (m, 2 H, $-CH_2-CO$); MS, *m/z* 204.1515 [$M^{+\cdot}$; $C_{14}H_{20}O$, 204.1514].

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found C, 82.25; H, 9.78.

***syn*-(1′*S*)-Spiro[cyclobutan-2-one-1,7′-(2′-*exo*-methylnorbornane)] (14).**[20] A solution of diphenylcyclopropylsulfonium tetrafluoroborate[25b] (350 mg, 1.11 mmol), 3 KOH pellets (crushed), and 10 mL of dry Me_2SO were reacted with 124 mg of (1*S*,4*R*)-*exo*-2(*R*)-methylbicyclo-[2.2.1]heptan-7-one (**15**),[3b] $[\alpha]_D$ -11° (*c* 0.7), 42% ee, in a sealed tube for 3 days (with days 1 and 3 at room temperature and day 2 at 48 °C. The reaction was quenched by addition of excess dilute (1:1) hydrochloric acid, poured into 200 mL of cold water, and extracted with petroleum ether (3 × 30 mL). The organic extracts were washed several times with water, dried ($MgSO_4$), evaporated to about 5 mL, and passed through 15 g of neutral alumina (Activity II). The desired sweet smelling product eluted with petroleum ether, following elution of diphenyl sulfide, and the combined fractions gave 45 mg (26%) of a colorless oil. It contained about 15% of an impurity which was removed by repeated preparative GC. The colorless oily ketone **14** (>99% pure) had the following: UV (isopentane) ϵ^{max}_{306} = 29; CD (isopentane) $\Delta\epsilon^{max}_{310}$ = 0.91, $\Delta\epsilon^{max}_{190}$ = 1.17 (corrected to 100% ee); IR (film) ν 1770, 1460, 1275, 1255, 1100, and 1065 cm^{-1}; ^{1}H NMR δ 1.04 (d, 3 H, J = 6 Hz, CH_3), 1.10-1.70 (m, 9 H), 1.83 (t, 2 H, J = 8 Hz, cyclobutanone CH_2), 2.80 (t, 2 H, J = 8 Hz, cyclobutanone $COCH_2-$); ^{1}H NMR (benzene-d_6) δ 1.22 (d, 3 H, J = 6 Hz, CH_3), 2.42 (t, 2 H, J = 8 Hz, $-CH_2CO$); MS, *m/z* 164.1206 [$M^{+\cdot}$, $C_{11}H_{16}O$, 164.1201]. Addition of Eu(thd)$_3$ to the $CDCl_3$ solution gave the following: ^{1}H NMR shifts δ 1.68 (d, 3 H, J = 6 Hz, CH_3), 3.50 (t, 2 H, J = 8 Hz, α-CH_2-), and 2.28 (t, 2 H, J = 8 Hz, β = CH_2-) with $\Delta\delta(CH_3)$ = 65 Hz, $\Delta\delta(\alpha\text{-}CH_2)$ = 70 Hz, and $\Delta\epsilon(\alpha\text{-}CH_2-)$ = 45 Hz.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.59; H, 9.51.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work and the National Science Foundation (CHE828216) for generous support of this work. We also thank Dr. S. L. Rodgers for preliminary studies with MM2 calculations.

[3.3]Metacyclophane: A Novel Synthesis and a Study of the Structure through X-ray Diffraction, Molecular Mechanics, and Solution NMR Analysis

M. F. Semmelhack,*[†,‡] J. J. Harrison,*[†,⊥] D. C. Young,[⊥] A. Gutiérrez,[‡] Shahin Rafii,[†] and Jon Clardy[†]

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14852, the Department of Chemistry, Princeton University, Princeton, New Jersey 08544, and the Gulf Research and Development Company, Pittsburgh, Pennsylvania 15116. *Received June 28, 1985*

Abstract: Coordination of 3-phenylpropionitrile with chromium hexacarbonyl followed by treatment of the resulting arene-chromium complex with lithium diisopropylamide and then iodine produced 1,12-dicyano[3.3]metacyclophane in a remarkable 84% yield. The process involves intermolecular nucleophilic addition to the coordinated arene, followed by cyclization of the dimer; iodine completes the addition/oxidation procedure for nucleophilic aromatic substitution for hydrogen. Reductive cleavage of the cyano groups produces the parent hydrocarbon, [3.3]metacyclophane. In the crystals, the molecule assumes a syn geometry with the bridging chains in a chair-chair conformation; however, the arene rings are tilted with respect to one another and slightly twisted. Molecular mechanics calculations find the same conformer as the energy minimum, with a similar tilt of the arene rings, but perfect C_{2v} symmetry (no twist). Two other conformations, syn(chair-boat) and syn(boat-boat), are within 1-2 kcal/mol of the lowest energy structure, while all conformers with the anti geometry are more than 6 kcal/mol higher. In solution, dynamic behavior is observed by variable-temperature ^{1}H NMR and ^{13}C NMR spectroscopy, attributed to interconversion of two syn conformers via a chair-boat motion of one of the three-carbon bridges. The barrier to isomerization is found to be 10-11 kcal/mol from both ^{1}H NMR and ^{13}C NMR data sets.

Considerable interest has existed in synthesizing and studying the properties of a class of compounds known as cyclophanes.[1] Of particular interest have been the [*m.n*]metacyclophanes because, in general, two different conformations, syn and anti, can exist (Figure 1). The terms synclinal and anticlinal have recently been used to describe the geometry for higher cyclophanes $n \geq 4$.[2]

In the parent [2.2]metacyclophane (**1**), the anti geometry is observed exclusively. The upfield shift of the aromatic proton H_i in **1** (δ 4.17) is a useful probe for the assignment of the anti geometry since H_i is constrained to lie directly over the π-electron cloud of the aromatic ring.[3] Syn geometries as typified by 2,11-dithia[3.3]metacyclophane (**2**) have H_i positioned downfield, in the usual range for arene hydrogens (e.g., δ 6.82 for **2**).[4] The NMR chemical shift criterion is useful for assigning geometries

[†] Cornell University.
[‡] Princeton University.
[⊥] Gulf Research and Development.

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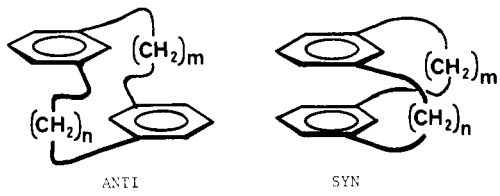


Figure 1. Syn and anti conformations of metacyclophanes.

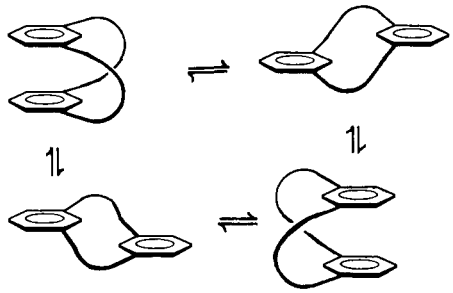
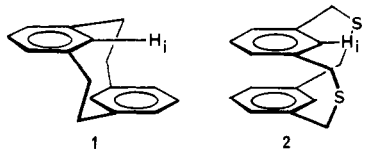


Figure 2. Conformational isomerism via syn–anti interconversion.

to other [*m.n*]metacyclophanes, but ambiguities often arise when substituents other than H are present.[5]



The anti arrangement for [*m.n*]metacyclophanes was thought to be generally the thermodynamically more stable conformation, partly because few *syn*-[*m.n*]metacyclophanes were reported in the early development of the area. Now numerous examples of *syn*- and *anti*-[*m.n*]metacyclophanes are known.[5b] The preference for syn or anti geometry, although not completely understood, is strongly dependent on both the lengths of the connecting chains (*m* and *n*) and on the substitution pattern of the cyclophane.[5]

Much interest has existed in understanding the dynamic processes of [*m.n*]metacyclophanes as observed by variable-temperature NMR spectroscopy.[5b] Dynamic behavior has been interpreted in terms of anti–anti, syn–syn, or syn–anti interconversions (Figure 2).[5b,6] Recent work has underscored the importance of conformational changes involving substituents and/or the alkyl bridging chains in [*m.n*]metacyclophanes, dithia[*m.n*]metacyclophanes, and dithia[*m.n*]metapyridinophanes.[4,5b,7] An anti, longitudinal conformational isomerism has also been reported.[7d]

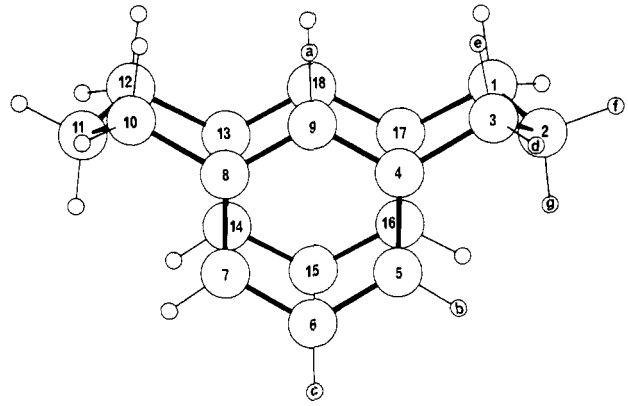


Figure 3. Perspective drawing from the X-ray model for **3**. Carbon atoms are labeled as in the X-ray discussion but the hydrogen atoms are given letters to facilitate the discussion of NMR spectral assignments.

The [3.3]metacyclophane (**3**) structure is a particularly interesting case for conformational isomerism, since both syn–anti and torsional motions in the connecting chains are expected to have energy barriers amenable to study by dynamic NMR spectroscopy. Remarkably, only one (very special) derivative[8] of this carbon skeleton was reported until 1976. The first synthesis of the parent structure (**3**), concurrent with the early stages of the work reported here, employed a double alkylation procedure to join two meta-disubstituted arenes into the [3.3]metacyclophane skeleton, with a yield of 5.4% in the key step.[9] A second preparation employed the traditional bis-thio-ether synthesis to give a dithia[4.4]metacyclophane in good efficiency followed by a thermal extrusion of sulfur dioxide for double ring contraction to **3** (2.7% yield).[10] A more effective process relies on double ring expansion by diazomethane addition to [2.2]metacyclophane-1,10-dione and led to **3** in about 18% yield overall from two 1,3-disubstituted arenes.[11] The ring expansion process also made available the three isomeric 1,11- 1,12-, and 2,11-dioxo-[3.3]metacyclophanes as a mixture from which pure isomers could be obtained by careful separation.[11] No studies of the static nor dynamic structural features of **3** have been reported.

In this article we describe a novel, efficient synthesis of the parent [3.3]metacyclophane and the first complete analysis of the structural features through studies of dynamic ^1H and ^{13}C NMR spectroscopy in solution, X-ray diffraction of a crystal, and molecular mechanics calculations. These results establish the syn geometry as the preferred arrangement in solution and in the crystal, and the dynamic behavior is interpreted in terms of the first reported example of chair–boat interconversion in [*m.n*]-metacyclophanes.

Results

Synthesis of [3.3]Metacyclophanes via (η^6-Arene)chromium Tricarbonyl Complexes. As part of the general study of cyclizations via nucleophile addition to arenes activated by coordination to the $Cr(CO)_3$ unit,[12] a remarkable preference was observed for [3.3]metacyclophane formation relative to a simple cyclization to a five-membered ring. Coordination of 4-phenylbutyronitrile with chromium hexacarbonyl produced complex **4** in 62% yield. Then the standard[13] addition/oxidation technique was triggered

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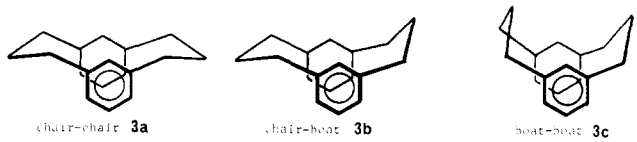
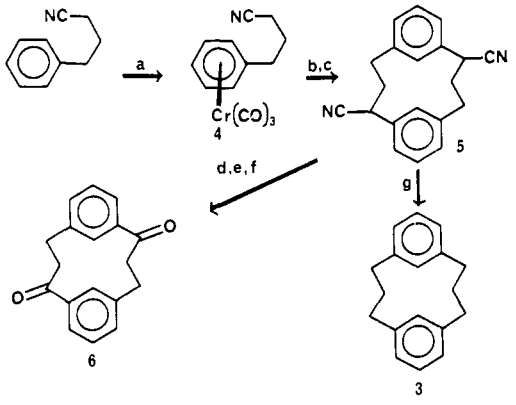


Figure 4. Conformational isomerism in the metacyclophane bridges.

by treatment with lithium diisopropylamide and completed by addition of excess iodine. The only product detected (84% yield after one recrystallization) was identified as 1,10-dicyano[3.3]-metacyclophane (**5**). Oxidative decyanation[14] produced the diketone **6** (68% yield). Treatment of **5** with sodium metal in liquid ammonia induced cleavage of the benzylic cyano groups and produced the parent hydrocarbon **3** in 91% yield as colorless crystals with mp 80–80.5 °C. The overall yield of 47% from 4-phenylbutyronitrile makes this process by far the most effective pathway to the [3.3]metacyclophane.



(a) $Cr(CO)_6$; (b) $LiN(iPr)_2$; (c) I_2; (d) $LiN(iPr)_2$; (e) O_2; (f) Na_2SO_3; (g) Na, NH_3.

X-ray Crystal Structure Determination. A computer generated perspective drawing of the final x-ray model of [3.3]metacyclophane (**3**) is given in Figure 3. As can be seen, the solid-state structure is roughly described as the chair–chair conformation (**3a**, Figure 4), but there are some significant distortions from this idealized conformational description. The first distortion is that best planes through the rings are not parallel but are tilted at an angle of 24° to each other. The sense of the tilt brings atoms C9 and C18 closer to each other so that their mean distance from the best plane of the other ring is 2.9 Å and atoms C6 and C15 further away from each other (4.0 Å). If this were the only distortion the hydrogen atoms on C9 and C18 would be approximately 2.4 Å apart. There is a second distortion, a twist of the aromatic rings by roughly 15° about an axis through the center of each ring. The effect of this twist is to move the hydrogens on C9 and C18 apart (2.7 Å). This twist also gives a chirality to the entire molecule, and since the space group is a chiral one, all molecules in the crystal have the same sense of chirality. It is not clear whether this solid-state resolution occurs in microcrystalline domains or throughout the entire crystal. In general bond distances and angles agree well with accepted values. The mean carbon–carbon interatomic distance in the aromatic rings is 1.389 (6) Å. The mean sp^2–sp^3 carbon–carbon distance is 1.519 (7) Å, and the mean sp^3–sp^3 distance is 1.538 (9) Å. The methylenes attached to the aromatic rings are not in the plane of the ring but 0.15 (2) Å out of the ring plane. All of the C–CH_2–C angles are significantly greater than 109°. The mean angle is 114.9 (13)°.

Molecular Mechanics Analysis of the Structural and Conformational Energetics of 3. EFF calculations were performed to determine the energy difference between the four most likely conformers of **3**: anti (C_{2v} symmetry), *syn*-**3a** (chair–chair), *syn*-**3b** (chair–boat), and *syn*-**3c** (boat–boat). The global minimum is

(14) Selikson, S. J.; Watt, D. S. *J. Org. Chem.* **1975**, *40*, 167.

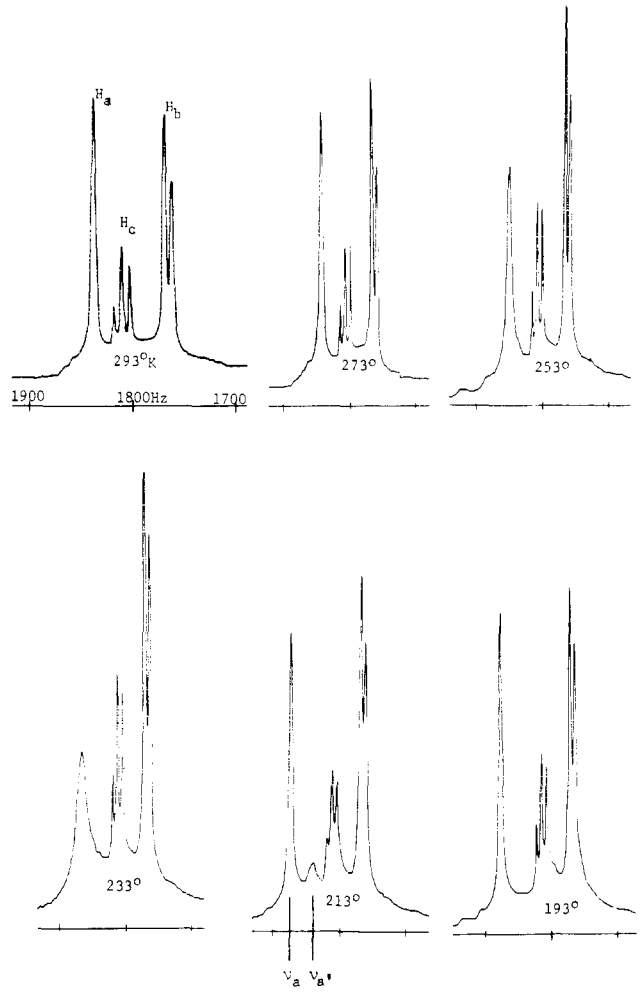


Figure 5. Arene proton region in the ^1H spectrum (270 MHz) for **3**.

3a, and the energies of the other minima relative to **3a** are the following: **3b**, 0.60 kcal/mol; **3c**, 1.07 kcal/mol; anti, 6.57 kcal/mol.

The calculated structure of **3a** (C_{2v} symmetry) and the X-ray structure compare well. As seen in the crystal structure, the arene rings of the calculated structure are tilted with respect to each other, but at an angle of only 18°. The distance between C_9 and C_{18} is 2.8 Å and that between C_6 and C_{15} is 3.7 Å. The calculated structure has exact C_{2v} symmetry and thus lacks the 15° twist seen in the crystal structure. The mean sp^2–sp^3 carbon–carbon distance is 1.512 Å, and the sp^3–sp^3 carbon–carbon distance is 1.542 Å, all in good agreement with the crystal structure. The C–CH_2–C angles are greater than 109°, with a mean value of 114.2°.

The barrier for conversion of **3a** to **3b** and **3c** was also probed by calculations. Typically, a saddle point was calculated by constraining two adjacent torsion angles, i.e., C_{ar}–CH_2–CH_2–CH_2 and CH_2–CH_2–CH_2–C_{ar}, at 0°, and allowing the rest of the molecule to relax. The constraints were then released and the structure was allowed to approach the saddle point by using the Variable Metric method while minimizing the forces. The full-matrix Newton–Raphson method was used to arrive at the single negative eigenvalue stationary point. The barrier for conversion of **3a** to **3b** is 11.95 kcal/mol while the barrier for **3b** → **3c** is almost identical, 12.32 kcal/mol.

Dynamic ^1H NMR Spectroscopy Study. A sample of **3** was examined by ^1H NMR spectroscopy at 200 and 270 MHz over the temperature range 181–294 °K. At 294 °K, a simple spectrum was obtained with the arene ring protons (Figure 5) appearing as the following series: singlet (δ 6.88, 2 H, H_a); distorted triplet (δ 6.74, 2 H, H_c, J = 7 Hz); and distorted doublet (δ 6.58, 4 H, H_b, J = 7 Hz). As shown in Figure 6, the benzylic protons

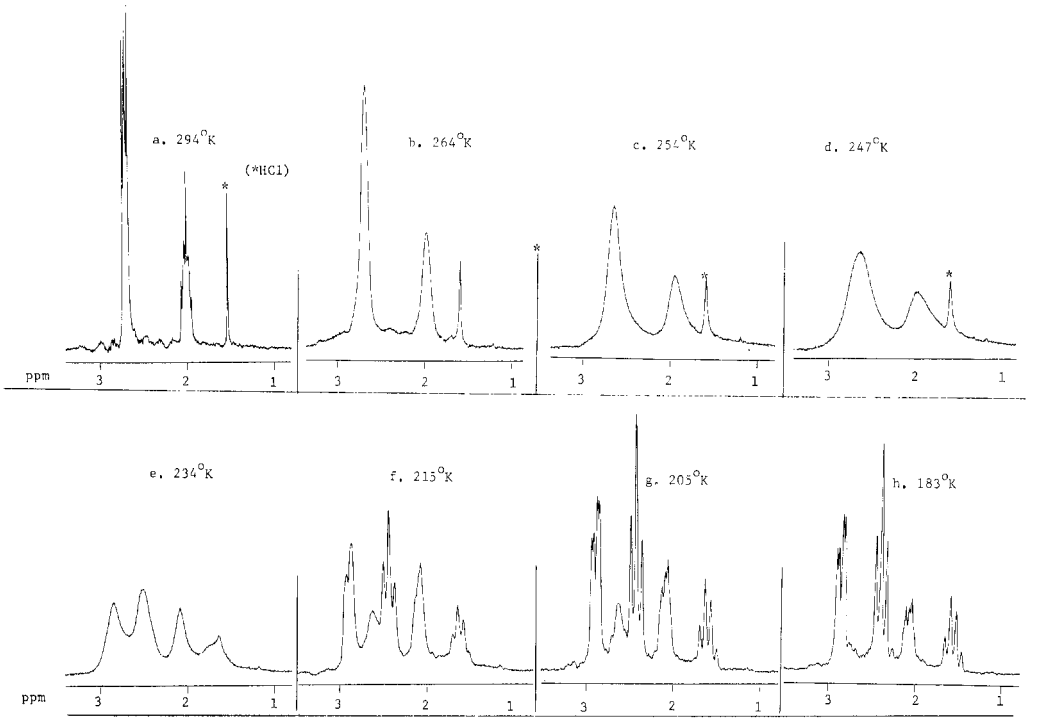


Figure 6. Aliphatic proton region in the ^1H NMR spectrum (200 MHz) for **3**.

Table I. ^1H NMR Spectral Parameters for the Major Isomer (**3a**) at 181 K

H, position (from Figure 3)	chemical shift (ppm)	multiplicity, area (coupling constant, Hz)
a	6.94	s, 2 H
b	6.52	d, 4 H (J = 7.0)
c	6.70	t, 2 H (J = 7.0)
c	2.88	dd, 4 H (J = 4, 12)
e	2.41	t, 4 H (J = 12)
f	2.10	dt, 2 H (J = 4, 12)
g	1.54	q, 2 H (J = 12)

appeared as a multiplet at δ 2.71 (8 H), while the C-2 and C-11 methylene groups gave another multiplet at δ 2.01 (4 H).

As the temperature was lowered, changes appeared in both the arene ring proton region and the aliphatic proton region. The signal assigned to H_a broadens and then resolves below −223 K into two broad signals of unequal intensity at δ 6.94 (ν_a, major) and 6.81 ($\nu_{a'}$, minor), as shown in Figure 5. At still lower temperatures, the signal at δ 6.81 disappears due to selective (reversible) crystallization of a minor isomer. This behavior has been noted previously for [3.3]paracyclophanes.[15] The benzylic protons ($H_{d,e}$, δ 2.71) and the C-2, C-11 methylene protons broaden at lower temperature and then resolve into four groups of peaks at the lowest temperature (183 K) as shown in Figure 6. The chemical shifts, coupling constants, and assignments for the major isomer are presented in Table I. The assignment of axial and equatorial protons for the major isomer (**3a**) follows from the known downfield shift of equatorial protons compared to axial protons[16] and from diagnostic coupling constants.[16] At 215 and 205 °K, the spectra show an additional broad peak at δ 2.7, which we assign to some or all of the aliphatic hydrogens in a minor isomer. The coalescence temperature for the benzylic region is about 244 K. The value of $\Delta G^{\ddagger}$ can be estimated in this dynamic process by using eq 1 to eliminate the rate of exchange at coalescence[6j] and by using the Eyring equation (eq 2).[17] The quantity

$$1.5\eta k_c = \frac{\pi\sqrt{2}}{2}(\Delta V^2 + 6J^2)^{1/2} \quad (1)$$

$$\Delta G^{\ddagger} = 4.576T(10.32 + \log T - \log k_c) \quad (2)$$

ΔV is the maximum frequency separation for protons d and e in Figure 3 when the effects of exchange are negligible (96 Hz), and J is the coupling constant (112 Hz). The value of $\Delta G^{\ddagger}$ at −244 °K is 11.5 kcal/mol.

Table II. ^{13}C NMR Chemical Shifts for **3** at 298 and 198 K

carbon[a]	chemical shift (ppm) at 298 K	chemical shift (ppm) at 198 K	
		major	minor
C_1(3,10,12)	δ 37.1	37.7	36.6
C_2(11)	δ 31.0	32.9	*b*
C_4(8,13,17)	δ 140.4	140.9	140.4
C_5(7,14,16)	δ 125.8	125.3	126.2
C_6(15)	δ 127.9	127.9	127.9
C_9(18)	δ 134.5	135.7	132.5

[a] Numbered as in Figure 3. [b] Minor isomer peak not observed above the spectral noise.

Table III. Chemical Shift of the Resonance for C-9(18) at Various Temperatures

temp (K)	ν_{obsd} (Hz)	% major	% minor	K	log K	ΔG (cal/mol)
309.5	2687	59	41	1.439	0.1580	−223.8
295.0	2689	62.5	37.5	1.667	0.2219	−299.6
275.0	2691	66	34	1.941	0.2878	−362.2
265.0	2692	67	33	2.030	0.3075	−372.9
247.0	2694	70	30	2.333	0.3679	−415.8
245.0	2694	70	30	2.333	0.3679	−412.5

Dynamic ^{13}C NMR Spectroscopy Study. Table II presents the ^{13}C NMR spectral assignments for fast equilibration (298 °K)

(15) (a) Anet, F. A. L.; Brown, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 2389–2391. (b) Benn, R.; Blank, N. E.; Haenel, M. W.; Klein, J.; Koray, A. R.; Weidenhammer, K.; Ziegler, M. L. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 44–45.

(16) Emsley, J. W.; Feeney, J.; Sutcliffe, L. H., Eds. "Progress in Nuclear Magnetic Resonance Spectroscopy"; Pergamon Press: New York, 1969; Vol. 5, Chapter 3 by Booth, H., p 49.

(17) Gordan, A. J.; Ford, R. A. "The Chemists Companion—A Handbook of Practical Data, Techniques, and References"; Wiley-Interscience: New York, 1972; p 136.

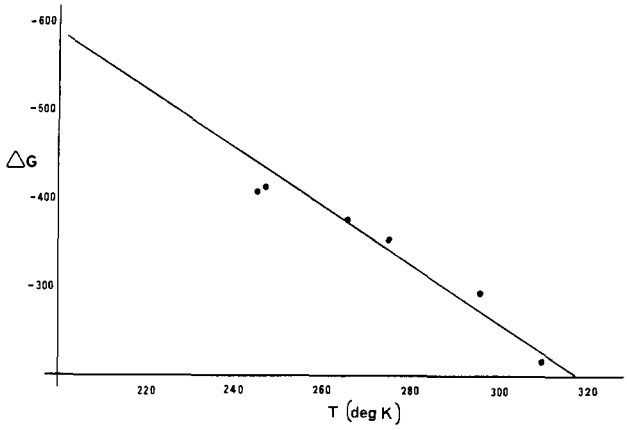


Figure 7. Plot of ΔG vs. temperature from ^{13}C NMR data at variable temperature.

Table IV. Extrapolated Populations and Kinetic Data

temp (K)	% **3a**	% minor	ν_{obsd} (Hz)	$W_{1/2}/h$	k (s^{-1})
247.0	70	30	2694	0.33	310
245.0	70	30	2694	0.33	305
242.0	71	29	2697	0.42	210
240.5	72	28	2700	0.50	120
233.0	73.5	26.5	2706	0.50	70
228.5	74	26	2708	0.46	60

and slow equilibration (198 °K). Parallel with the ^1H NMR experiment, there is peak broadening as the temperature is lowered; four signals broaden and then each splits into two resonances, one signal broadens but is not further resolved, and one signal remains a sharp singlet at all temperatures studied. Again, at the lowest temperature, the minor isomer crystallizes and complicates a direct measurement of the relative amounts of the major and minor isomers. In order to calculate the energy difference between the two observable isomers, we examined the chemical shift of the resonance for C-9(15) (Table II) as a function of temperature over the range 309.5–245.0 °K (Table III). This range is well above the temperature of coalescence and selective precipitation. Using eq 3 which relates population of the major isomer to observed chemical shift and eq 4 which relates ΔG with equilibrium constant, we obtain the values listed in Table III. The chemical shifts for the resonance for C-9(15) in the pure major isomer (2713 Hz) and for the pure minor isomer (2649 Hz) are taken from the low temperature limiting spectra (198 K). Plotting ΔG vs. T (Figure 7) gives $\Delta H = -1.1 \pm 0.2$ kcal/mol and $\Delta S = -2.8 \pm 0.9$ eu for the equilibration of the two observable isomers.

$$\%\ \mathbf{3a} = \frac{\nu_{obsd} - \nu_{minor}}{\nu_{3a} - \nu_{minor}} \quad (3)$$

$$\Delta G = -RT \ln K_{eq} \quad (4)$$

A line-shape analysis was attempted utilizing the ^{13}C NMR resonance for C-9(18) over the temperature range 228.5–247.0 K. Experimental difficulties include the long time required to record the spectrum and the low signal-to-noise ratio which we observed for the coalescing peaks. We used the criteria of peak position (ν_{obsd}) and width at half-height/height ratio ($W_{1/2}/h$) to match simulated and observed spectra. The population of each isomer in the region of coalescence was determined by extrapolating the ΔG vs. T plot to the appropriate temperature (Table IV). For each temperature, the rate constant was adjusted until a best fit was obtained with use of a standard poly site mutual exchange program. The ln k vs. $1/T$ relationship was plotted and the least-squares slope intercept obtained (Figure 8, Table V). We calculate $E_a = 10.8 \pm 2.1$ kcal/mol and log $A = 12.0 \pm 3.9$ eu.

Discussion

The parent [3.3]metacyclophane exists in the crystal as the syn isomer, with approximately the chair–chair arrangement of the

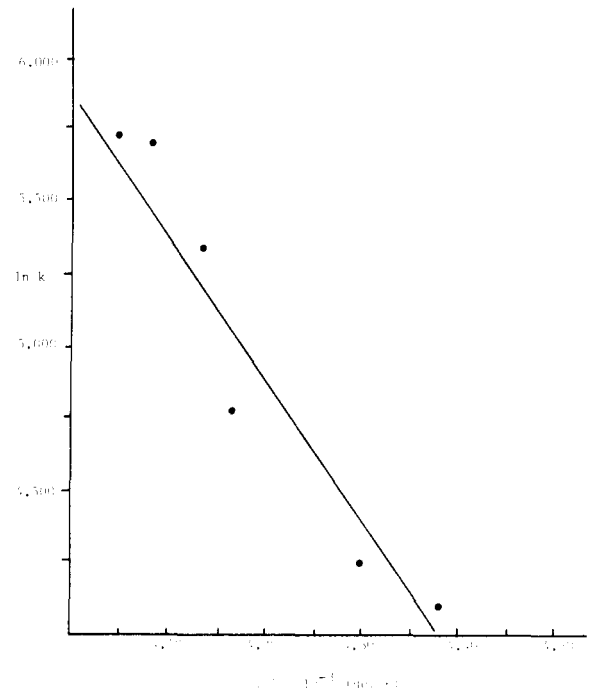


Figure 8. Plot of ln k vs. $1/T$ from ^{13}C NMR data at variable temperature.

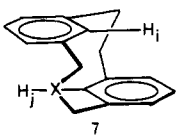
bridging trimethylene chains, as represented by **3a**. This is in contrast with [2.2]metacyclophane which prefers the anti geometry but parallel with the structure of 2,11-dithia[3.3]metacyclophane and other metacyclophanes which exist in the syn arrangement in the solid.[5,7] There is a significant tilt of the benzene rings, which tends to bring the unique hydrogens at C-9 and C-18 very close if C_{2v} symmetry is maintained. A further distortion is apparent in the crystal, by twisting of the benzene rings about an axis through the center of each ring, which may be due to crystal packing forces or to relief of crowding at the C-9/C-18 hydrogens. The NMR spectral data in solution and the molecular mechanics calculations suggest the simple structure **3a** with C_{2v} symmetry; the calculations do support the picture of tilted rings. An anti conformation in solution is ruled out by the chemical shift of the C-9/C-18 hydrogens (δ 6.88); no evidence of the strong upfield shift expected to the C-9 hydrogen in an anti arrangement[3] was obtained. The substantial energy difference (6.6 kcal/mol) calculated between the syn conformer **3a** and the anti conformer is consistent with an undetectable (by NMR) population of the latter.

However, variable-temperature ^1H NMR and ^{13}C NMR spectroscopy did suggest rapid conformational isomerism in **3**. Two forms of **3** are detected, equilibrating fast at 25 °C and slow at temperatures below about −50 °C. The detectable conformers show distinct chemical shift differences and both are assigned the syn arrangement, based on the C-9/C-18 hydrogen signals at δ 6.94 and 6.81 in the "frozen" mixture. Three reasonable conformers (**3a–c**) differ by way of chair–boat interconversion, not unlike cyclohexane. The molecular mechanics calculations suggest an order of stability of **3a** > **3b** > **3c**, but with rather small energy differences. The structure **3a** is fully consistent with the ^1H NMR spectral data for the major isomer (Table I). Assignment of the structure of the minor isomer (**3b** or **3c**) is not obvious. On the basis of the conformer energy calculations, all three syn conformers are expected to be significant in the NMR spectral data in the low temperature limiting spectra. Two explanations for the observation of only two isomers seem most reasonable: either the chemical shifts of the undetected isomer (both ^1H and ^{13}C NMR) are essentially identical with one of the observed isomers *or*, more likely, the third isomer appears at concentrations below the thresholds for detection (perhaps less than 2% as abundant as the major isomer). This implied energy difference of about 2–2.5 kcal/mol is not outside the uncertainty of the calculated energy

differences. Since the observed changes are between two different chemical species and since neither of them shows the characteristic ^{1}H NMR behavior of an anti isomer, isomerizations of the type syn–syn and syn–anti are ruled out. The energy difference between the isomers (1.1 kcal/mol) obtained from the ^{13}C NMR data is nicely consistent with the molecular mechanics calculation on **3a**/**3b**/**3c**.

The barrier to isomerization of **3a** of about 11 kcal/mol, obtained by analysis of both the ^{1}H NMR and ^{13}C NMR data sets, corresponds favorably with the conformational barrier in cyclohexane (10.5 kcal/mol),[18] with the barrier calculated for both **3a** → **3b** and **3b** → **3c** (about 12 kcal/mol in each case), and with the barrier for chair–boat interconversion in [3.3]paracyclophane (10 kcal/mol).[15b]

Note on Dynamic Processes in Other [*m.n*]Metacyclophanes. Variable-temperature NMR studies of [*m.n*]metacyclophanes have recently been reviewed by Mitchell.[5b] A number of syn–anti and anti–anti interconversions are reported, but not the chair–boat equilibration process now established for **3**. The evidence for anti–anti interconversion in substituted [3.2]metacyclophane, for example, has been obtained from coalescence of the AB pattern[6a,6d] of the benzylic protons or chemical averaging of the H_i, H_j hydrogens in **7**. Similarly, coalescence of the AB pattern for benzylic $-CH_2-$ groups has been taken as evidence for syn–anti isomerization of various [*m.n*]metacyclophanes.[5b]



7

X = S, SO_2, SO, $C(CO_2Et)_2$

In general, for all *syn*- and *anti*-[*m.n*]metacyclophanes where either *m* or *n* equals 3, a chair–boat interconversion of the 3-carbon bridge scrambles axial and equatorial hydrogens and thus also may result in coalescence of the AB benzylic $-CH_2-$ pattern. In the *anti*-[*m.n*]metacyclophane, chair–boat interconversion also scrambles H_i/H_j (Figure 9). It may be appropriate to reassign the conformational isomerism responsible for the variable-temperature NMR data in many [*m.n*]cyclophanes. The chair–boat motion may be generally the predominant process.

Experimental Section

General. ^{1}H NMR spectra were recorded on Perkin-Elmer R24B (60 MHz), Varian EM-390 (90 MHz), Varian XL-200 (200 MHz), and Bruker WP-270 (270 MHz) spectrometers. Chemical shift positions are in ppm downfield from internal tetramethylsilane. ^{13}C NMR data were obtained on a Varian CFT-20 (20 MHz) spectrometer; chemical shift positions are in ppm relative to internal deuteriochloroform (taken as δ 77.00). NMR multiplicities are reported by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; M, multiplet; br, broad. J = coupling constant in hertz. Temperature calibration for variable-temperature ^{1}H NMR was carried out by measuring the chemical shift difference on the signals from a methanol sample. Infrared spectra were recorded on a Perkin-Elmer Model 237 or Model 299 instrument. Only the strongest and/or structurally most important peaks are reported for the IR. Analytical thin-layer chromatography (TLC) was performed with use of Machery Nagel and Co. Polygram pre-coated plastic sheets with a 0.25-mm layer of silica gel and a fluorescent indicator.

All solvents were ACS reagent grade and were not further purified unless otherwise noted. Tetrahydrofuran (THF) was distilled immediately before use from sodium benzophenone ketyl under argon. Diisopropylamine, dichloromethane, and hexamethylphosphortriamide were distilled from calcium hydride, under reduced pressure where appropriate, and stored over Linde 4Å molecular sieves.

Preparation of [η^6-(3-Cyanoprop-1-yl)benzene]tricarbonylchromium(0) (4). Following a general procedure,[19] a mixture of chromium hexacarbonyl (20.00 g, 0.110 mol, Pressure Chemical Co.), 4-phenylbutyronitrile[20] (5.00 g, 34.7 mmol), and 250 mL of *p*-dioxane (freshly distilled from sodium benzophenone ketyl) was placed in a 500-mL three-necked round-bottom flask equipped with an air condenser (70 × 2 cm vertical tube capped with a stopcock attached to an argon/vacuum inlet). The system was placed under argon by alternately evacuating to boil the solvent and filling with argon (3×). The mixture was heated at gentle reflux under a slight positive pressure of argon. After 60 h, the mixture was cooled in an ice bath, opened to the air, and filtered, and the filtrate was concentrated by rotary evaporation. The residue was purified by column chromatography on silica gel (hexane–dichloromethane, 3:1) to give yellow crystals, 4.92 g (62% yield, mp 59–60 °C), of complex **4**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.0–5.4 (m, 5 H, arene-H), 2.1–2.6 (t overlapping m, 4 H), 1.5–2.0 (m, 2 H); IR ($CHCl_3$) 2260, 1960, 1800 cm^{-1}; MS (EI, 70 eV) parent at *m/e* 281.015. Calcd for $C_{13}H_{11}NO_3{}^{52}Cr$: 281.017.

Preparation of 1,12-Dicyano[3.3]metacyclophane (5). To a three-necked round-bottom flask equipped with a magnetic stirring bar, a serum cap, and a 3-way stopcock leading to argon/vacuum was added via syringe THF (15 mL) and 2,2,6,6-tetramethylpiperidine (0.37 mL, 2.21 mmol). The mixture was placed under argon and cooled to −78 °C, and a solution of *n*-butyllithium in hexane (1.15 mL of 2.00 M, 2.30 mmol) was added dropwise over 1 min. The resulting solution was allowed to stir at 0 °C for 0.5 h. It was again cooled in a dry ice bath, and HMPA (10 mL) was added slowly followed by dropwise addition (0.5 min) of a solution of complex **4** (590 mg, 2.00 mmol) in THF (5 mL). The resulting solution was allowed to stir at −78 °C for 1 h and at 0 °C for 1 h. Then, with the mixture at −78 °C, a solution of iodine (2.0 g) in THF (7 mL) was added dropwise over 2–3 min. The mixture was allowed to stir at 25 °C for 8 h, then it was diluted with ether (100 mL), and then the mixture was washed sequentially with 10% aqueous sodium bisulfite solution (2×), water (5×), saturated aqueous sodium bicarbonate (1×), and water (1×). The ether solution was dried ($MgSO_4$) and concentrated to produce a light yellow solid. Recrystallization from dichloromethane–ethanol afforded colorless crystals of **5** with mp 153–155 °C (241 mg, 84% yield). ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.23–2.56 (m, 4 H), 3.01 (t, J = 7.0 Hz, 4 H), 3.96 (t, J = 7.0 Hz, 2 H), 6.81 (s, 6 H), 7.06 (s, 2 H); IR (mull) 2250, 1620, 800, 710, 705 cm^{-1}; MS (EI, 70 eV) *m/e* 286. Calcd for $C_{20}H_{18}N_2$: 286.

Anal. Calcd: C, 83.85; H, 6.33; N, 9.82. Found: C, 83.87; H, 6.28; N, 9.80.

Oxidative Decyanation of 5 To Give Diketone 6. To a solution of lithium diisopropylamide (1.1 mmol) in THF (15 mL) at −78 °C under argon was added dropwise over 0.5 min a solution of bis-nitrile **5** (143 mg, 0.50 mmol) in THF (5 mL). The mixture was stirred at 0 °C for 0.5 h and then cooled to −75 °C and a stream of dry oxygen gas was bubbled through the mixture until the yellow color disappeared (about 20 min). An aqueous solution of sodium sulfite (2 mL, 1.0 M) was added and the mixture was allowed to stir at 0 °C for 0.5 h. The crude mixture was partitioned between ether and water and from the ether solution was obtained a yellow solid. Recrystallization from dichloromethane–ethanol produced diketone **6** as colorless crystals: 90 mg, 65% yield; mp 134–136 °C; ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 8 H), 6.99–7.25 (m, 8 H); IR ($CHCl_3$) 1680, 1600, 1580, 800, 690, cm^{-1}; MS (Ei, 70 eV) parent at *m/e* 264.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.70; H, 6.18.

Preparation of [3.3]Metacyclophane (3). The bis-nitrile **5** (43.7 mg, 0.154 mmol) was stirred in a mixture of THF (0.5 mL) and liquid ammonia (20 mL) at reflux under a dry ice cooled condenser. To this was added sodium metal (16 mg, 0.60 mmol) in several pieces. A blue color appeared and was quickly consumed. After addition was complete, excess water was added carefully, and the ammonia was evaporated with a slow stream of argon. The residue was extracted with chloroform, and the chloroform solution was dried ($MgSO_4$) and concentrated to leave a yellow oil. Short path distillation (120 °C bath, 0.01 torr) gave a colorless solid, 33.2 mg, 91% yield, mp 80–80.5 °C (lit.[9] mp 79–80 °C).

Variable-Temperature NMR Spectra. A sample of [3.3]metacyclophane (90 mg) was dissolved in a mixture of CS_2 and CD_2Cl_2 (1.0 mL, 1:1 (v/v)). Spectra (^{1}H) were run on a Bruker 270-MHz NMR spectrometer and are reported in Figure 2. A second sample of [3.3]-metacyclophane (10 mg) was dissolved in CD_2Cl_2 (0.5 mL), and spectra were obtained at 200 MHz (reported in Figure 1). Variable-temperature ^{13}C NMR spectra were run on a Varian CFT-20 (20 MHz) with a solution of [3.3]metacyclophane in a mixture of CS_2:CD_2Cl_2 (1:1 (v/v)). A spectra width of 600 Hz, a filter bandwidth of 500 Hz, an acquisition time of 1.5 s, a pulse width of 7 μs, and 1800 data points with 0-s pulse

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(19) For a discussion and leading references, see: Semmelhack, M. F.; Hall, H. T.; Farina, R.; Yoshifuji, M.; Clark, G.; Bargar, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 3535.

(20) Tanaka, M. *Nippon Kagaku Zasshi* **1961**, *82*, 242. Cf. *Chem. Abstr.* **1961**, *56*, 10037g.

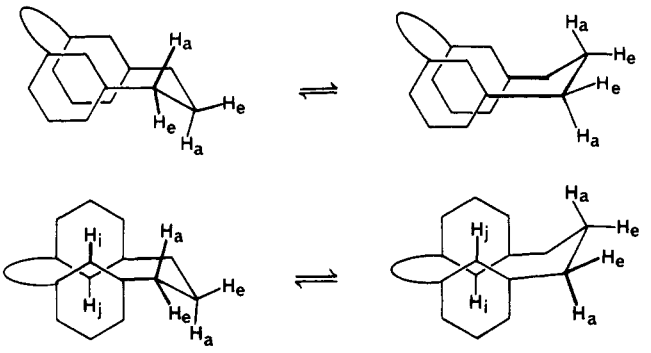

Figure 9.

delay were used. The transmitter offset was 75 and decoupler offset at 52 for the VT spectra. Typically, 1500–2000 transients were run.

Single-Crystal X-ray Structure Determination of [3.3]Metacyclophane (3). Crystals of **3** were grown by slow evaporation of CH_2Cl_2–isooctane solutions. A roughly cubic crystal with edges ~0.4 mm was cut from a larger crystal and used in all subsequent experiments. Because of the tendency of [3.3]metacyclophane (**3**) to sublime, all X-ray measurements were conducted at low temperature, approximately −40 °C. Preliminary X-ray photographs displayed monoclinic symmetry and accurate lattice constants of a = 8.0006 (4) Å, b = 9.013 (4) Å, c = 9.401 (4) Å, and B = 97.75 (4)° were determined from a least-squares fit of 15 diffractometer measured 2θ values. The crystal density, 1.16 g/cm^3, indicated that two molecules of **3** made up the unit cell. The systematic extinctions were consistent with either space group $P2_1$ or $P2_1/m$. In the latter space group, [3.3]metacyclophane would have to use one of the crystallographic symmetry elements and have either a crystallographic mirror plane or inversion center. We initially explored this option but were frustrated in finding a satisfactory model. We then turned to space group $P2_1$ (vide infra). All unique diffraction maxima with $2\theta \leq 55°$ were collected on a computer-controlled four-circle diffractomer using variable speed, 1° ω-scans and graphite monochromated Mo K$\bar{\alpha}$ radiation (0.71069 Å). Of the 1005 reflections measured in this fashion, 823 (82%) were judged observed ($F_o \geq 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects.[21] We were unable to find a phasing model employing space group $P2_1/m$, but in space group $P2_1$ a phasing model was found uneventfully by using a multisolution tangent formula approach.[21] All non-hydrogen atoms were easily located on the initial E synthesis. Hydrogen atoms were located on a ΔF synthesis after partial refinement of the non-hydrogen positions and thermal parameters. Block-diagonal least-squares refinements with anisotropic non-hydrogen atoms and fixed isotropic hydrogens have converged to a conventional crystallographic residual of 0.034 for the observed data. Further results of the crystallographic experiment are available and are described in the supplementary material paragraph.

Table V. Data for ln k vs. $1/T$ Plot from ^{13}C Data for **3**

k (s^{-1})	ln k	T (K)	$1/T$
310	5.7376	247.0	0.00405
305	5.7213	245.0	0.00408
210	5.3480	242.0	0.00413
120	4.7884	240.5	0.00416
70	4.2490	233.0	0.00429
60	4.0950	228.5	0.00438

Molecular Mechanics Calculations. The EFF calculations were performed with BIGSTRN-3[22] using Allinger's MM2 force field[23] and minimizing with variable metric and Newton–Raphson techniques. The optimization was considered converged when the root-mean-square value of the atom movement was less than 10^{-6} Å. No restrictions were placed on the conformations. The X-ray parameters were used as input into BIGSTRN-3 and the result was the C_{2v}. This implies that there is no minima structure with the same kind of twist as the X-ray structure.

Acknowledgment. The formation of metacyclophane rings via arene–chromium complexes was discovered by Y. Thebtaranonth and L. Keller as part of a larger study of nucleophile addition to arene–metal complexes, and we are grateful for their preliminary work including the procedures for compounds **4** and **5**. This work was supported by research grants (NSF CHE 78-18776 to M.F.S.; NIH CA 24487 to J.C.) and a postdoctoral fellowship (NSF to J.H.). Supplementary NMR data were collected with cooperation of the Gulf Research Laboratories, to whom we are grateful.

Registry No. 3, 62155-71-9; **4**, 62259-88-5; **5**, 62276-32-8; **6**, 98923-00-3; chromium hexacarbonyl, 13007-92-6; 4-phenylbutyronitrile, 2046-18-6.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, interatomic distances, and interatomic angles for **4** and a structure (4 pages). Ordering information is given on any current masthead page.

(21) All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were the following: REDUCE and UNIQUE, data reduction programs by M. E. Leonwicz, Cornell University, 1978; MULTAN 78, MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1978 and 1980; DIRDIF written by P. T. Beurskens et al., University of Nijmegen, Netherlands, 1981; MITHRIL, an automatic solution package written by C. J. Gilmore, University of Glasgow, Scotland, 1983; BLS78A, an anisotropic block diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

(22) This program was developed by K. Mislow and co-workers and is being prepared for submission to QCPE. For further description see: Bürgi, H.-B.; Hounshell, W. D.; Nachbar, R. B., Jr.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1427.

(23) Allinger, N. L.; Yuh, Y. H. *QCPE* **1981**, *13*, 395. Two modifications were used for the C_{Ar}–C_{Ar} bonds: 1° = 1.3937 Å and k_s = 8.0677 mdyn/Å.