The First Conformational Study of Dithia[3.1.3.1]metacyclophanes, [2.1.2.1]Metacyclophanes, and [2.1.2.1]Metacyclophanedienes by Variable Temperature NMR Spectroscopy[1]

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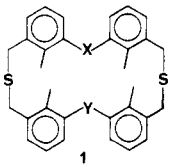
The stereochemistry of the cyclophanes **1A–C**, **2A–C** (major isomers), and **8A–C** has been assigned to be of type **2e**, and these cyclophanes have been shown to all undergo a conformational process of type **12**. The barriers for this process have been estimated from their variable temperature ^{1}H NMR spectra to be in the range 40–86 kJ/mol depending on the bridges. These are the first examples of the higher metacyclophanes with clearly defined conformational properties.

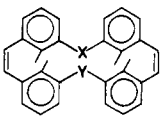
Introduction

In the immediately preceding accompanying paper[2] we describe the syntheses and some chemical reactions of cyclophanes **1A,B** and **2A,B** and how by our failure to



1

	X	Y
A:	C=O	C=O
B:	C=O	CH_2
C:	CH_2	CH_2
D:	CHOH	CH_2

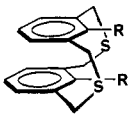


2

	X	Y
A:	C=O	C=O
B:	C=O	CH_2
C:	CH_2	CH_2

form a bridge between the X and Y groups, we concluded that our assignment of the stereochemistry of these compounds was probably wrong. This paper describes our investigations of the variable temperature NMR spectra of these and several derived compounds to arive at the correct stereochemistry for this interesting group of cyclophanes.

While the stereochemical aspects of cyclophanes have been of particular interest over the last two decades,[3,4] most attention has been paid to the lower members, and in particular to [2.2]- and [3.3]metacylophanes which can adopt either syn or anti conformations as shown in **3** and **4**.



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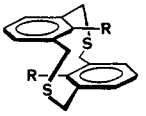

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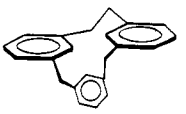
Higher [2^n]metacyclophanes have been known for some time and, when $n \geq 3$, are conformationally mobile,[4,5] though with unknown conformations. Knowledge of the conformations of other higher metacyclophanes at the start of this work was scanty. The [2.1.1]-, the [2.2.0]-, and the [2.0.2.0]metacyclophanes **5**,[6] **6**,[7] **7**,[8] respectively, were



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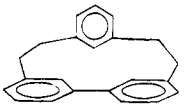

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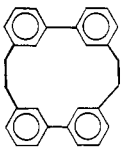

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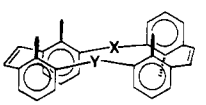
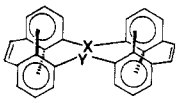
known, and on the basis of variable temperature nuclear magnetic resonance (vtNMR) data show some conformational motion. However, without further study, it is still not clear even at this time whether this motion is merely that of bridge wobbles or whether the molecules are undergoing a major conformation change of the type **3** ⇌ **4**.

We were led to assign incorrect stereochemistries, namely the stepped structures **2a** and **2b** for each of

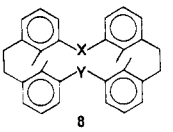


2a



2b

2A,2B, partly because of the fortuitous "fit" of ^{1}H NMR data of the two isomers each of **2A** and **2B** for these stepped structures together with the fact that the literature contains little information on the conformations of higher cyclophanes but overwhelming amounts of data for compounds of type **3** and **4**. The problem was really only fully resolved when the fully reduced compound **8C** became available.



8

	X	Y
A:	C=O	C=O
B:	C=O	CH_2
C:	CH_2	CH_2

Stereochemistry Reassignments for 1, 2, and 8. Reassignment of the stereochemistry of compound **2B**,

(1) (a) Taken from the doctoral thesis of Yee Hing Lai, University of Victoria, Sept, 1980. (b) For a preliminary report, see: Mitchell, R. H.; Lai, Y. H. *Tetrahedron Lett.* **1980**, *21*, 2633.

(2) Mitchell, R. H.; Lai, Y. H. *J. Org. Chem.*, preceding paper this issue.

(3) Reviews: Smith, B. H. "Bridged Aromatic Compounds"; Academic Press: New York, 1964. Vögtle, F.; Neumann, P. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 73; *Synthesis* **1973**, 85. Misumi, S., Otsubo, T. *Acc. Chem. Res.* **1978**, *11*, 251. Vögtle, F.; Höhner, G. *Top. Curr. Chem.* **1978**, *74*, 1.

(4) For an extensive and recent review on the conformational properties of cyclophanes studied by NMR spectroscopy see: Mitchell, R. H. In "Cyclophanes"; Keehn, P., Rosenfeld, S., Eds.; Academic Press: New York, 1983; Chapter 4.

(5) Flammang, R.; Figeys, H. P.; Martin, R. H. *Tetrahedron* **1968**, *24*, 1171. Paioni, R.; Jenny, W. *Helv. Chim. Acta* **1969**, *52*, 2041. Burri, K.; Jenny, W. *Ibid.* **1967**, *50*, 1978.

(6) Sato, T.; Wakabayashi, M.; Hata, K.; Kainosho, M. *Tetrahedron* **1971**, *27*, 2737.

(7) Vögtle, F. *Liebigs Ann. Chem.* **1969**, *728*, 17.

(8) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046; *J. Org. Chem.* **1980**, *45*, 4498. Gutsche, C. D.; Dhawan, B.; No, K.H.; Muthukrishan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

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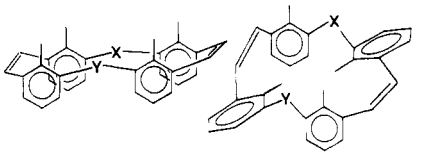
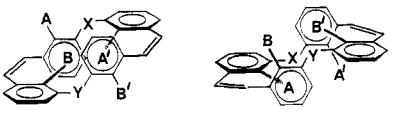
discussed in the previous paper, has to account for the facts that for the major isomer the methyl protons appear as two pairs of singlets, one set shielded at δ 1.18 and 1.09 and the other normal (for a toluene) at δ 2.37 and 2.28, that the aromatic protons appear as two sets, one set shielded at δ 6.68–6.13 (characteristic for *syn*-benzene rings) and the others normal at δ 7.47–6.98, and that the methylene bridge occurs as an AB (J = 15 Hz) as do the vinyl protons with a coupling constant of 11.5 Hz, normal for a cis alkene. (In fact **2a** (X = CO, Y = CH_2) would have two sets of vinyl protons, however we had assumed an accidental shift degeneracy.) Clearly the all anti and all syn conformers **2b** and **2c** are not consistent with the number of methyl sig-



2c 2d

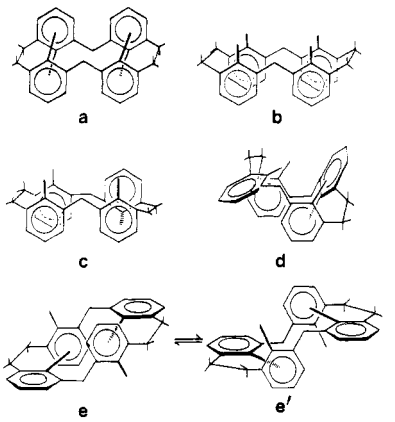


2e 2f

nals, nor is the very open **2d** which would also be expected to show one set of *syn*-methyl signals and two sets of vinyl protons, and as well because of the now wide spacing of the benzene rings, the latter would not be expected to have shielded ring protons. Conformer **2d** is in fact an "opened out" form of **2c**, obtained by rotation of the bridges. The data however are consistent with conformers **2e** and **2f**, which are enantiomers, and have in one conformer methyls A and B′ pointing to the center of the ring and hence are shielded by the opposite (B or A′) ring, while in the other conformer the other methyls A′ and B are now pointed in and shielded, while A and B′ are normal. This is consistent with the −20 °C ^{1}H NMR data and suggests a 50:50 mixture of each enantiomer is frozen out at this temperature. At higher temperatures, these conformers should interconvert, presumeably either through **2d** or an equivalent open conformer. Then coalescence of the methylene, methyl, and aromatic protons would be expected to occur, which they do at 120 °C. In principle methyl groups A and B should have different chemical shifts at higher temperatures also, however they both appear at δ 1.75.

Thus we believe that the major isomer of cyclophane **2B** (mp 291–293 °C) exist as a pair of conformational enantiomers **2e** ⇌ **2f**, and that at low temperatures this conformational equilibrium can be frozen out. Moreover in these conformers the carbonyl (X) and the methylene bridge (Y) groups are always very far apart, an explanation for our inability to couple these bridges; also the exposed carbonyl group of **2e**,**2f** vs. the sheltered group of **2a** would be much more available for external nucleophilic attack.

Similar arguments can be made for the dicarbonyl compound **2A**: the major isomer, mp 318–320 °C, showed two singlets for the methyl protons at δ 2.41 and 1.14, two sets for the aromatic protons at δ 7.50–7.15 and 6.70–6.43, and a singlet in this case for the vinyl protons at δ 6.82, also consistent with **2e** ⇌ **2f** (X = Y = CO). The variable temperature ^{1}H NMR spectra for this compound are available as Figure S5. Unfortunately, both of these compounds were too insoluble to obtain satisfactory ^{13}C NMR spectra. However, the fully reduced compound **8C** (see below for synthesis) was more satisfactory. Its variable



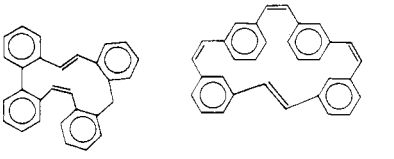
a b c d e e′

Figure 1. Relatively unstrained conformers of **8C**.

temperature ^{1}H NMR spectra have been published in our preliminary report[1b], and at low temperature (−20 °C) show the internal methyl protons as singlets at δ 2.38 and 1.19, the methylene bridges as an AB quartet at δ 3.68 (Δδ = 0.6), and the aromatic protons as one set shielded at δ 6.6–6.0 (an AB_2 pattern) and one set normal at δ 7.4–7.0. At higher temperatures (120 °C) all of these signals collapse to give a simpler spectrum, the methyls appearing at δ 1.76, the methylene bridge at δ 3.69, the aromatics at δ 7.1–6.5, and the $-CH_2CH_2-$ bridge at δ 2.95. Of the conformers shown in Figure 1, a, b, and d are readily eliminated on the same grounds as previously for **2A**. Since the $-CH_2CH_2-$ bridges could not be clearly seen, e ⇌ e′ (AA′BB′) could not be distinguished from c (two approximate AA′BB′). However, the ^{13}C NMR spectrum (Figure S9) of this more soluble compound left no doubt: only two $-CH_2CH_2-$ bridge carbon signals, one $-CH_2-$ bridge signal, and two $-CH_3$ signals could be seen, consistent with e ⇌ e′, whereas c would be expected to show four and two and four signals, respectively. It is unlikely that all of these would suffer shift degeneracy. Taken collectively the evidence, chemical and spectroscopic, for the **2e** ⇌ **2f** or e ⇌ e′ (Figure 1) stereochemistry is convincing, but can only be easily confirmed by an X-ray structure.

However, subsequent work by others[8] on the [1^4]metacyclophanes gives support to our conclusions.

Having established the structure of the major isomers of **2A** and **2B**, clearly the question then arises as to the stereochemistry of the minor isomers. The ^{1}H NMR spectrum of the minor isomer of **2B**, mp 286–288 °C, shows only one type of methyl proton at δ 1.18, only normal aromatics at δ 7.64–7.06, only a singlet for the $-CH_2-$ protons at δ 4.27, and an unclear AB system for the vinyl protons (only the central lines visible), and is not temperature dependent over the range −100 °C to +150 °C. Since this was not consistent entirely with any of **2a** to **2f**, the possibility of a trans double bond was considered. While no [2.2]metacyclophanene (or diene) is known with trans double bonds, they do occur in higher cyclophanes, for example **9**[9] and **10**.[10] Although the coupling constant



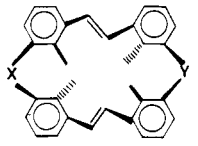
9 10

(9) Gamliel, Al.; Willner, I.; Rabinovitz, M. *Synthesis* **1977**, *410*.
(10) Thulin, B.; Wennerstrom, O.; Somfai, I. *Acta Chem. Scand. Ser. B* **1978**, *B32*, 109.

Table I. 90 MHz ^{1}H NMR Data (δ) for Compound 11A-C

proton	11A	11B	11C
Ar H	7.76–7.15 (m, 12 H)	7.64–7.06 (m, 12 H)	7.38–7.06 (m, 12 H)
CH=CH	6.8 (s, 4 H)	6.59, 6.56 inner lines of AB (4 H)	6.49 (s, 4 H)
CH_2		4.27 (s, 2 H)	4.20 (s, 4 H)
Ar CH_3	1.30 (s, 12 H)	1.18 (s, 12 H)	1.14 (s, 12 H)

of the vinyl protons for this isomer of **2B** could not be determined, its IR spectrum did show absorptions near 960 cm^{-1} consistent with a trans double bond. Conclusive evidence was obtained by reduction (see below) of this isomer of **2B** to **11C**, mp 305–307 °C, which showed a

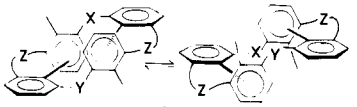


11

	X	Y
A:	C=O	C=O (minor isomer, 2A)
B:	C=O	CH_2 (minor isomer, 2B)
C:	CH_2	CH_2

strong IR band at 965 cm^{-1}, and a simple ^{1}H NMR spectrum consisting of a singlet at δ 1.14 for the methyl protons, a singlet for the methylene protons at δ 4.20, and a singlet for the vinyl protons at δ 6.49, consistent with the highly symmetrical all-trans structure **11** shown. By analogy the minor isomers of **2A** and **2B** thus have the reassigned stereochemistries depicted by **11A** and **11B**, respectively. The relevant spectral data of these three compounds are collected in Table I.

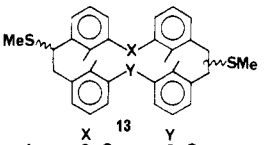
Generality of the Conformational Process 2e ⇌ 2f. With the conformational process **2e ⇌ 2f** established for the major isomers of **2A** and **2B** and for compound **8C**, we decided to investigate the generality of this process for cyclophanes of type **12**.



12

	X	Y	Z
A: (1C)	CH_2	CH_2	CH_2SCH_2
B: (1B)	CO	CH_2	CH_2SCH_2
C: (1A)	CO	CO	CH_2SCH_2
D: (2C)	CH_2	CH_2	CH=CH
E: (major isomer, 2B)	CO	CH_2	CH=CH
F: (major isomer, 2A)	CO	CO	CH=CH
G: (8C)	CH_2	CH_2	CH_2CH_2
H: (8B)	CO	CH_2	CH_2CH_2
I: (8A)	CO	CO	CH_2CH_2

Syntheses. Compounds **1A** and **1B** were described in the previous paper.[2] Reduction of **1B** with $NaBH_4$ in CF_3COOH by using Gribble's method[11] was incomplete: however, if the carbonyl group was first reduced to the alcohol **1C** (not isolated) by using $NaBH_4$ in wet THF, and this was then treated with $NaBH_4$ in CF_3COOH, thiacyclophane **1C**, mp 290–292 °C, was obtained in 89% overall yield. Its structure was confirmed by a strong MH^+ peak at m/e 509 in its mass spectrum, and a clear region around 1700 cm^{-1} in its IR spectrum. At room temperature the ^{1}H NMR spectrum showed three singlets for the Ar_2CH_2, $-CH_2S-$, and $-CH_3$ protons at δ 3.84, 3.63, and 1.78, respectively, and thus the compound is mobile. A similar two step reduction of **2B** (the major isomer) yielded 88% of cyclophanediene **2C**, mp 311–313 °C. In its ^{1}H NMR spectrum, **1C** showed a very broad signal for the methyl protons at room temperature, which suggested that a conformational process was occurring, and that room temperature was close to coalescence. At higher temperatures the expected singlets were obtained at δ 3.69, 2.95, and 1.76 for the Ar_2CH_2, $-CH_2S-$ and $-CH_3$ protons, respectively. The first attempts to prepare **8B** were carried out by Raney nickel reduction of **13B**.[2] However, some-



13

	X	Y
A	C=O	C=O
B	C=O	CH_2
C	CH_2	CH_2

what surprisingly, treatment of **13B** with W-7 Raney nickel in aqueous ethanol under prolonged reflux conditions gave the hydrocarbon **8C**, mp 282–284 °C. The IR spectrum indicated an absence of a C=O group, and its mass spectrum gave a MH^+ peak at m/e 445 confirming **8C**. We have subsequently explored this Raney nickel reduction of aryl carbonyls and have shown[12] that as long as at least one aryl is conjugated to the carbonyl, it can be directly reduced under neutral conditions in refluxing aqueous ethanol in good yields to an arylmethane ($ArCH_2-$), and this thus represents a useful alternative to the Clemmenson (acidic), Wolf–Kishner (basic), or Mozingo (thioketal) reductions.

In view of the fact that organic sulfides should be more readily reduced with Raney nickel,[13] and that ethanol is a poorer hydrogen donor than water,[14] we anticipated that use of absolute ethanol for shorter reaction times should not reduce the carbonyl group. Indeed, reaction of **13B** with W-7 Raney nickel for 4 h in absolute ethanol at reflux yielded 89% of cyclophane **8B**, mp 261–262 °C. Reduction of cyclophane **13A** under similar conditions likewise afforded an 85% yield of **8A**, mp 299–300.5 °C. These two compounds also showed broad methyl peaks at room temperature in their ^{1}H NMR spectra. Thus, all of compounds **12A–I** were now on hand to undertake variable temperature ^{1}H NMR studies.

Fluxional Behavior of 12A–I. Each of the cyclophanes **12A–I** was examined by ^{1}H NMR under variable temperature conditions, and the pertinent low and high temperatures data are presented in Table II. (Full vtNMR data, Figures S1–S10 are available from the authors on request and have been deposited as supplementary figures.) In our opinion each of the cyclophanes is undergoing a conformational process represented by **12** and discussed in detail for **8C** (e ⇌ e′, Figure 1) above. In each case, with the exception of **12C** which was too insoluble to obtain low temperature spectra, two sets of methyl protons could be seen for the frozen low temperature conformer, one set shielded by about 1.3 ppm by being between the faces of the parallel benzene rings and the other set normal, and in each case, with the exception of **12F** where the coalescence temperature was >150 °C, a

(11) Gribble, G. W.; Kelly, W. J.; Emery, S. E. *Synthesis* **1978**, 763.

(12) Mitchell, R. H.; Lai, Y. H. *Tetrahedron Lett.* **1980**, *21*, 2637.

(13) Patai, S. "The Chemistry of the Thiol Group"; Wiley: New York, 1974, Part 2, Chapter 2.

(14) Sakai, K.; Watanbe, K. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1548. Sakai, K; Ishige, M.; Kono, H.; Motoyama, I.; Watanbe, K.; Hata, K. *Ibid.* **1968**, *41*, 1902.

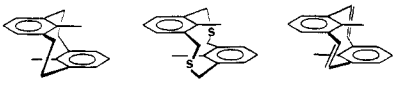
Table II. 90 MHz ^{1}H NMR Data[a] for the Cyclophanes 12A–I in $CDCl_3$ (Low Temperataure) and Hexachlorobutadiene (High Temperature)

phane	T, °C	Ar H, δ	central CH_2, δ	bridging CH_2 or CH=, δ	Ar CH_3, δ
12A	−100	7.3–6.2 (m)	4.4–2.9 (m)		2.42 (s), 1.16 (s)
	0	7.2–6.7 (m)	3.84 (s)	3.63 (s)	1.78 (s)
12B	−100	7.7–6.3 (m)	4.3–3.1 (m)		2.75 (s), 2.48 (s), 1.34 (s), 1.20 (s)
	−20	7.4–6.8 (m)	3.97 (s)	3.76 (s)	2.00 (s), 1.88 (s)
12C[d]	+35	7.4–7.2 (m)		3.67 (s)	1.88 (s)
12D	−50	7.5–7.2 (m) 6.7–6.1 (m)	AB system: δ_A 3.94 (d, J = 15 Hz), δ_B 3.34 (d, J = 15 Hz)	6.83 (s)	2.22 (s), 1.11 (s)
	+150	7.0–6.7 (m)	3.78 (s)[c]	6.8 (s)[b]	1.64 (s)
12E	−20	7.5–7.0 (m) 6.7–6.1 (m)	AB system: δ_A 4.09 (d, J = 15 Hz), δ_B 3.51 (d, J = 15 Hz)	AB system: δ_A 6.87, δ_B 6.77 (d, J = 11.5 Hz)	2.37 (s), 2.28 (s), 1.18 (s), 1.09 (s)
	+120	7.2–6.7 (m)	3.76 (s)[c]	b	1.75 (s)[c]
12F[e]	0	7.5–7.2 (m) 6.7–6.4 (m)		6.82 (s)	2.39 (s), 1.11 (s)
12G	−20	7.4–7.0 (m) 6.6–6.0 (AB_2)	AB system: δ_A 3.98 (d, J = 14 Hz), δ_B 3.39 (d, J = 14 Hz)	3.6–2.4 (m)	2.38 (s), 1.18 (s)
	+120	7.1–6.5 (m)	3.69 (s)	2.95 (s)	1.76 (s)
12H	−40	6.8–5.9 (m) 7.5–7.0 (m)	AB system: δ_A 3.99 (d, J = 15 hz), δ_B 3.43 (d, J = 15 Hz)	3.5–2.6 (m)	2.52 (s), 2.40 (s), 1.19 (s), 1.14 (s)
	+150	7.2–6.5 (m)	3.74 (s)	3.01 (s)	1.84 (s)[c]
12I	−40	7.5–7.1 (m) 6.9–6.2 (m)		3.6–2.2 (m)	2.54 (s), 1.15 (s)
	+150	7.2–6.7 (m)		2.98 (s)	1.85 (s)[c]

[a] For full spectra, see supplementary figures (deposited). [b] Overlapped with aromatic protons. [c] A broad singlet. [d] Too insoluble for low temperature studies. [e] Coalescence temperature >150 °C.

single methyl proton peak at higher temperatures, which appeared at the average position of the low temperature sets in each case. Similar changes were likewise observed for the Ar_2CH_2 protons, and the bridging $-CH_2CH_2-$ protons, providing additional evidence for the process proposed. Additionally, hydrogenation of the dienes **11C** and **12D** over palladium on charcoal both afforded the same saturated cyclophane **12G**, (=**8C**) with identical variable temperature behavior as the sample obtained by reduction of **13B**. This suggests that only the one conformer **2e** ⇌ **2e′** is involved as the preferred fluxional process.

It is particularly interesting that the chemical shifts of the methyl groups in **12G** (δ 1.18), **12A** (δ 1.16), and **12D** (δ 1.11) are almost identical, in contrast to those of **14** (δ



14 **15** **16**

0.56),[15] **15** (δ 1.30),[16] and **16** (δ 1.52).[17] In the latter three cases sufficient geometric change probably[4] occurs as the bridges are changed to pull the methyl group progressively out of the most intense shielding region of the opposite benzene ring. Clearly no such change occurs with the more flexible cyclophanes **12**.

Reasonably one might expect the cyclophanes with the longer $-CH_2SCH_2-$ bridges to be the more flexible. This hypothesis was investigated next.

The Barrier to the Fluxional Process. The coalescence temperature method to estimate the transition state free energy at the coalescence temperature ($\Delta G_c^{\ddagger}$) is not only commonly used in cyclophane chemistry,[4] but has recently been shown by us[18] to be as good as full line shape analysis in relatively simple systems. In the cases under study, the methyl protons, which appear as singlets, show line widths (<10 Hz), much smaller than their chemical shift difference (>100 Hz), and hence reasonably good $\Delta G_c^{\ddagger}$ (±<1kJ) values should be obtained if T_c can be determined within 3 K.[19] Moreover, since the molecules under study (**12A–I**) all have identical methyl substituents, and the same fluxional process is understudy, $\Delta S^{\ddagger}$ can be reasonably assumed to be more or less constant throughout the series, and so comparisons should be able to be made. Thus $\Delta G_c^{\ddagger}$ was calculated using the equation[21,22]

$$\Delta G_c^{\ddagger}\ (\text{kJ/mol}) = 2.303 \times 8.314 T_c(10.319 - \log_{10} k_c + \log_{10} T_c)$$

Table III. Data Used To Calculate $\Delta G_c^{\ddagger}$ for 12A–I

compd	Δν, Hz[a]	TΔν, °C[b]	T_c, °C[c]	$\Delta G_c^{\ddagger}$, kJ/mol
12A	113.4	−100	−70	39.4
12B	121.1	−100	−73	38.7
12C		too insoluble		
12D	99.9	−50	15	57.1
12E	108.9	−20	70	68.2
12F	115.2	0	>150	>85
12G	108.0	−20	60	66.2
12H	116.6	−40	75	69.1
12I	125.1	−40	90	72.0

[a] Separation of methyl proton signals at 90 MHz using 15–25 mg of compound in 0.5 mL of solvent ($CDCl_3$ or hexachlorobutadiene. [b] Temperature at which Δν was measured. [c] Coalescence temperature for methyl proton signals.

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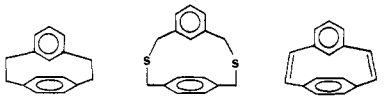
(16) Mitchell, R. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1547.
(17) Blattmann, H. R.; Meuche, D.; Heilbronner, E.; Molyneux, R. J.; Boekelheide, V. *J. Am. Chem. Soc.* **1965**, *87*, 130.
(18) Dixon, K. R.; Mitchell, R. H. *Can. J. Chem.* **1983**, *61*, 1598.
(19) This is the specified accuracy of our spectrometer (Perkin-Elmer R32B), and it has been checked by calibration using the methanol shift method.[20]
(20) Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York, 1972; p 303.

where $k_c = (\pi/\sqrt{2})\Delta\nu$ and the results are given in Table III.

Clearly changing the bridges from $-CH_2SCH_2-$ to $-CH{=}CH-$ to $-CH_2CH_2-$, e.g., in a comparison of **12A** with **12D** with **12G**, substantially increases the barrier in each of the three sets of samples, consistent with results found in the smaller cyclophanes,[4] e.g., for **17**, **18**, and **19**, $\Delta G_c^{\ddagger}$ values found[23] were 87, 35, <27 kJ/mol, respectively.

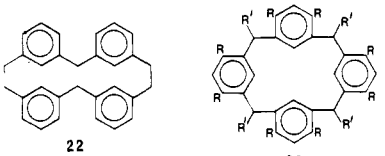


17 19 18

Changes associated with changing the one carbon bridges of **12** from sp^3 (CH_2) to sp^2 (C=O) are smaller and less regular, being about 3 kJ/mol in **12G** → **12H** → **12I**, for example, though larger for the cyclophanedienes **12D,E,F** with the maximum barrier being reached in **12F** where all the bridges involve sp^2 atoms. Interestingly, in the [4.1]cyclophanes **20** and **21** no significant change in barrier ($\Delta G_c^{\ddagger} \approx 82$ kJ/mol) was observed in going from **20** to **21**.[24]

20 21

Unfortunately, not many higher cyclophanes are known with internal substituents. We have already commented above that the unsubstituted cyclophane **7** is mobile, and thus from the data we have here, it would suggest that the parent cyclophane **22** should also be mobile at normal



22 23

temperatures. The barriers found in our examples **12** are similar to those for the noninternally substituted but smaller [1[4]]cyclophanes **23** ($\Delta G_c^{\ddagger}$ = 64 kJ/mol).[8] Several higher [2[n]]paracyclophanes are known,[4] and these adopt a variety of conformations, but lacking subsituents make comparisons with **12** somewhat awkward.

Conclusions

The conformational process has been established for a number of [3.1.3.1]- and [2.1.2.1]metacyclophanes, **12**. The barrier for the conformational process depends on the nature of the bridges and in the examples studied has been found to range from about 40–85 kJ/mol, being largest for all sp^2 atom bridges. These are the first examples of higher metacyclophanes where the process has been clearly established and is different to the lower members of the family, e.g., the [2.2]- or [3.3]metacyclophanes.[25]

Experimental Section

The same general notes apply as in the preceding paper.[2]

9,16,25,32-Tetramethyl-2,18-dithia[3.1.3.1]metacyclophane (1C, 12A). A mixture of $NaBH_4$ (2.8 mg, 0.076 mmol) and thiacyclophane **1B**[2] (19.9 mg, 0.038 mmol) in wet THF (50 mL) was heated under reflux for 12 h. After the mixture had cooled, dilute HCl was added and then ether. The organic layer was washed, dried, and evaporated. The residue was mixed thoroughly with powdered $NaBH_4$ (14.4 mg, 0.38 mmol) and added in small portions to CF_3COOH (50 mL) at 0 °C under N_2 with vigorous stirring. After stirring for a further 15 min, the mixture was decomposed with aqueous $NaHCO_3$ solution and then extracted with dichloromethane. The organic extract was washed, dried, and evaporated and the residue directly recrystallized from benzene to give colorless crystals of **1C** (**12A**): 17.1 mg (89%); mp 290–292 °C; ^1H NMR (90 MHz) see Table II; IR (KBr) 1460, 788, 736, 725 cm^{-1}; MS (CI) MH^+, *m/e* 509 (90), 447 (100), 247 (84). Anal. Calcd. for $C_{34}H_{36}S_2$: C, 80.26; H, 7.13. Found: C, 80.55; H, 7.23.

8,15,23,30-Tetramethyl[2.1.2.1]metacyclophane (8C, 12G). Mixed isomers of cyclophane **13B**[2] (50 mg, 0.09 mmol) were added to 95% ethanol (25 mL) containing excess of W-7 Raney nickel (ca. 9 mmol) and the mixture was heated under reflux for 12 h. The nickel was filtered and the solvent evaporated. The residue was recrystallized from cyclohexane to give colorless crystals of **8C** (**12G**): 34.2 mg (85%); mp 282–284 °C; ^1H NMR see Table II; IR (KBr) 1445, 776, 732, 719 cm^{-1}; MS (CI) MH^+, *m/e* 445 (100), 238 (34), 224 (55), 222 (55). Anal. Calcd. for $C_{34}H_{36}$: C, 91.84; H, 8.16. Found: C, 91.89; H, 8.11.

8,15,23,30-Tetramethyl-9-oxo[2.1.2.1]metacyclophane (8B, 12H). Mixed isomers of cyclophane **13B**[2] (22.0 mg, 0.04 mmol) were added to absolute ethanol (15 mL) containing excess W-7 Raney nickel (ca. 0.4 mmol) and the mixture was gently heated under reflux for 3.5 h. The nickel was filtered and the solvent evaporated. The residue was filtered in benzene through a short column of silica gel and then was recrystallized from cyclohexane to give 16.4 mg (89%) of colorless crystals of **8B** (**12H**): mp 261–262 °C; ^1H NMR see Table II; IR (KBr) 1666 (C=O), 1460, 1263, 1100, 800, 773, 736, 719 cm^{-1}; MS (CI) MH^+, *m/e* 459 (14), 275 (17), 248 (19), 247 (100). Anal. Calcd. for $C_{34}H_{34}O$: C, 89.04; H, 7.47. Found: C, 89.35; H, 7.69.

8,15,23,30-Tetramethyl-9,24-dioxo[2.1.2.1]metacyclophane (8A, 12I). Mixed isomers of cyclophane **13A**[2] (22.6 mg, 0.04 mmol) were added to absolute ethanol (15 mL) containing excess W-7 Raney nickel (ca. 0.4 mmol), and the mixture was gently heated under reflux for 4 h. The nickel was filtered, the solvent was evaporated, and then the residue was filtered in benzene through a short column of silica gel. The product was recrystallized from benzene/cyclohexane to give 16.0 mg (85%) of colorless crystals of **8A** (**12I**): mp 299–300.5 °C; ^1H NMR see Table II; IR (KBr) 1665 (C=O), 1455, 1274, 928, 789, 758, 740, 723 cm^{-1}; MS (CI) MH^+, *m/e* 473 (12), 458 (12), 451 (17), 329 (34), 287 (12), 275 (28), 248 (18), 247 (100). Anal. Calcd. for $C_{34}H_{32}O_2$: C, 86.40; H, 6.82. Found: C, 86.12; H, 6.79.

8,15,23,30-Tetramethyl[2.1.2.1]metacyclophane-*cis*,*cis*-1,16-diene (2C, 12D). $NaBH_4$ (5.7 mg 0.15 mmol) was added to a solution of the cyclophane **2B** (major isomer)[2] (**12E**) (34.1 mg, 0.075 mmol) in wet THF (100 mL) and the mixture was heated under reflux for 14 h. After the mixture had cooled, dilute HCl was added and then dichloromethane. The organic layer was washed, dried, and evaporated. The residue was then mixed thoroughly with powdered $NaBH_4$ (28.5 mg, 0.75 mol) and added in small portions to CF_3COOH (50 mL) at 0 °C under N_2 with vigorous stirring. After a further 20 min, aqueous $NaHCO_3$ solution was added and then dichloromethane. The organic layer was washed, dried, and evaporated, and the residue recrystallized from cyclohexane/hexane to yield 29 mg (88%) of colorless crystals of **2C** (**12D**): mp 311–313 °C; ^1H NMR see Table II; IR (KBr)

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(22) Measurements of $\Delta\nu$ and T_c should be made in the same solvent, however even though chemical shifts in these systems vary somewhat between hexachlorobutadiene and chloroform,[23] we have observed that differences in shifts between peaks in the same sample have only very small variations. Moreover a difference in $\Delta\nu$ of 10 Hz at T_c = 173 K, only changes $\Delta G_c^{\ddagger}$ by ca. 0.2 kJ/mol.
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1449, 840, 810, 778, 764, 756, 728, 718 cm^{-1}; MS (CI) MH^+, *m/e* 441 (31), 275 (17), 247 (100). Anal. Calcd. for $C_{34}H_{32}$: C, 92.68; H, 7.32. Found: C, 92.64; H, 7.36.

8,15,23,30-Tetramethyl[2.1.2.1]metacyclophane-*trans*,-*trans*-1,16-diene (11C). $NaBH_4$ (2.7 mg, 0.07 mmol) was added to a solution of cyclophane **2B** (minor isomer)[2] (15.9 mg, 0.035 mmol) in wet THF (50 mL) and the mixture heated at reflux for 12 h. After the mixture had cooled, dilute HCl was added and then dichloromethane. The organic layer was washed, dried, and evaporated, and the residue was mixed thoroughly with powdered $NaBH_4$ (13.5 mg, 0.35 mmol) and added in portions to CF_3COOH (30 mL) at 0 °C under N_2 with vigorous stirring. After a further 20 min, aqueous $NaHCO_3$ solution was added and then dichloromethane. The organic layer was washed, dried, and evaporated, and the residue was recrystallized from cyclohexane/hexane to give 12.5 mg (81%) of colorless crystals of **11C**: mp 305–307 °C; ^1H NMR (90 MHz) δ 7.38–7.06 (m, 12 H, Ar H), 6.49 (s, 4 H, —CH=), 4.20 (s, 4 H, CH_2), 1.14 (s, 12 H, Ar CH_3); IR (KBr) 1458, 965 (*trans*-CH=CH), 848, 779, 769, 759, 710 cm^{-1}; MS (CI) MH^+, *m/e* 441 (10), 425 (10), 275 (20), 249 (39), 247 (100). Anal. Calcd. for $C_{34}H_{32}$: C, 92.68; H, 7.32. Found: C, 92.70; H, 7.30.

Hydrogenation of Dienes 2C and 11C to 8C (12G). 30% Pd/C (3 mg) was added to a solution of the cyclophanediene **2C** or **11C** (15 mg) in dry benzene (10 mL), which was then stirred under 1 atm of H_2 at 20 °C for 24 h. Removal of catalyst and then solvent yielded in both cases quantitative samples of **8C (12G)** identical with the previously obtained samples (mp, ^1H NMR, MS).

Registry No. 1A, 90133-68-9; **1B**, 75404-52-3; **1C**, 90133-67-8; **2A**, 90133-71-4; **2B**, 90133-70-3; **2C**, 90133-69-0; **8A**, 90133-73-6; **8B**, 90133-72-5; **8C**, 75397-87-4; **11A**, 90133-74-7; **11B**, 90133-75-8; **11C**, 90133-76-9.

Supplementary Material Available: Full variable temperature NMR data for compounds **12** and figures S1–S10 (10 pages). Ordering information is given on any current masthead page.

Charge-Shift Probes of Membrane Potential. Synthesis

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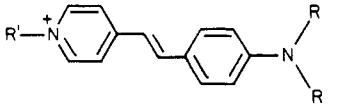
We are reporting two general synthetic approaches to a number of (aminostyryl)pyridinium dyes and their heterocyclic analogues which are of interest as electrochromic probes for membrane potential. The two routes which involve palladium-catalyzed coupling or aldol condensation permit considerable structure variations to be introduced in the dyes. Some spectral properties of the dyes are discussed.

The synthesis of cyanine, merocyanine, and styryl dyes has been based largely on a key condensation step between the heterocyclic nuclei. These dyes are especially useful as sensitizers in the photographic industry, and their syntheses have been thoroughly reviewed.[1] Hundreds of these dyes are commercially available.

Cohen[2] and Tasaki[3] were the first to discover voltage-dependent changes in fluorescence or transmittance characteristics of the squid giant axon which had been stained with a variety of dyes. It soon became apparent that the electrical properties of a variety of cell and membrane preparations could be studied in this way.[4]

We have been interested in the styryl class of dyes because of the possibility that they would respond to membrane potential changes by an electrochromic mechanism.[5,6] The latter requires that the dyes should provide a response time which is able to follow the fastest of physiological events, and should be operative on a wide variety of membrane preparations.

A number of (*p*-aminostyryl)pyridinium dyes **1** have



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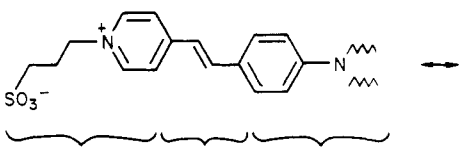
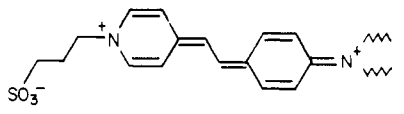
been tested on model membrane systems and do indeed appear to respond to voltage pulses via electrochromism.[7,8] Such electrochromic dyes are amenable to theoretical design and are of intrinsic physical-chemical interest apart from the biological applications. The synthesis of these dyes has closely followed the aldol condensation strategy.[9] In an effort to explore chromophores with more extended π-systems and dyes with unusual side chains it has become necessary to expand the aldol condensation methodology as well as to develop other general dye syntheses.

The chromophoric system that has been most useful in our studies of membrane potential probes is exemplified by structure **1a**. These molecules possess at their polar



A



B

1a

hydrophilic end a pyridinium salt moiety preferably in the form of an electrically neutral zwitterion sulfonate (part a). This heterocyclic moiety is conjugated via an unsatu-

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