Tetrahedron, Vol. 40, No. 21, pp. 4401 to 4413, 1984.
Printed in Great Britain

0040-4020/84 $3.00 + .00

SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 8,11-DIHALO[5]METACYCLOPHANES

LEONARDUS W. JENNESKENS, FRANCISCUS J. J. DE KANTER, LUCAS A. M. TURKENBURG, HENRICUS J. R. DE BOER, WILLEM H. DE WOLF and FRIEDRICH BICKELHAUPT*

Vakgroep Organische Chemie, Vrije Universiteit
De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

(*Received in UK* 27 *July* 1984)

Abstract - The synthesis of the 8,11-dihalo[5]metacyclophanes 1b-1d (halogen = chlorine or bromine) from 1,2-dimethylenecycloheptane (2) is described. Spin saturation transfer and line shape analysis of the temperature dependent ^{1}H NMR spectra showed 1b-1d to occur in two conformations A (85-89%) and B (15-11%, respectively). The conformation of the pentamethylene bridge was fully analyzed from vicinal proton coupling constants which obey the Karplus relation inspite of severe distortions of the carbon valence angles. The thermodynamic parameters of the ground and transition state were determined for the equilibrium between the conformers A and B and are discussed in terms of steric interactions in these highly strained molecules.

INTRODUCTION

Investigations on short-bridged [n]meta- and [n]paracyclophanes are intriguing for many reasons. In the first place, the extremely high strain of such molecules makes their synthesis by conventional approaches such as ring closure reaction impossible, so that alternative synthetic strategies have to be developed. Indeed, the shortest known members of both series, i.e. [5]metacyclophane (1a)[1] and [6]paracyclophane[2-5] and their derivatives have been obtained by novel and specific pathways in which, with one exception,[2] the bridge was in position before the aromatic ring was formed. A second interesting aspect of such compounds resides in their stereochemistry. The influence of strain on the bending of the benzene rings and on the conformation of the oligomethylene bridges has been shown to lead to rather unusual features.[1f,4d,5a] Finally, the consequences of strain and of the unusual geometries on the chemical reactivity are beginning to receive attention.[1a,c,d,3,5b]

In preliminary studies, we have deduced from physical and chemical properties as well as from MNDO calculations, that 1a is indeed a rather strained molecule. The crystal structure determination of 1b,[1f] the 8,11-dichloro derivative of 1a, has recently confirmed the highly non-planar geometry of its benzene ring. This ring is boat-shaped with a bending angle at the bow of 26.8° and at the stern of 12°; the benzylic bonds are bent out of plane by 48° in the opposite direction. The pentamethylene bridge showes widened C-C-C- angles and adopts a puckered conformation A (Fig. 1). In solution, however, a temperature dependent ^{1}H-NMR spectrum was observed for 1b which was interpreted in terms of two conformations A and B (Fig. 1) of comparable energy.[1e]

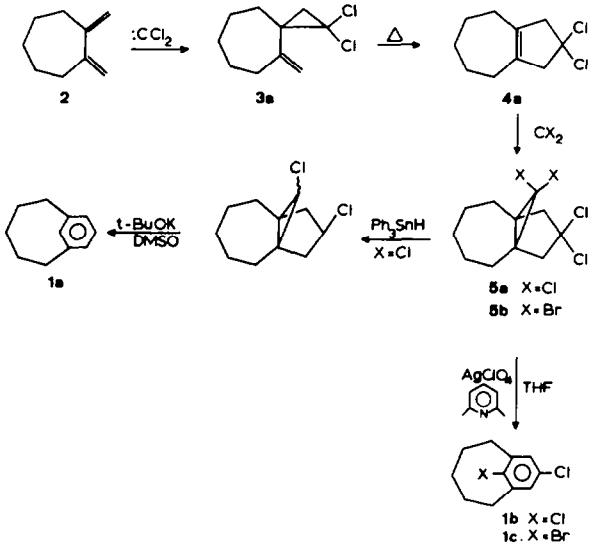
In order to gain insight into the factors responsible for these phenomena, and in particular to understand the influence of the substituent at C(11), we decided to synthesize also some bromine analogues of 1b. In this paper, we present details on the syntheses of 1b, and of the new compounds 11-bromo-8-

-chloro[5]metacyclophane (1c) and 8,11-dibromo[5]metacyclophane (1d), and a conformational analysis of their pentamethylene bridges.

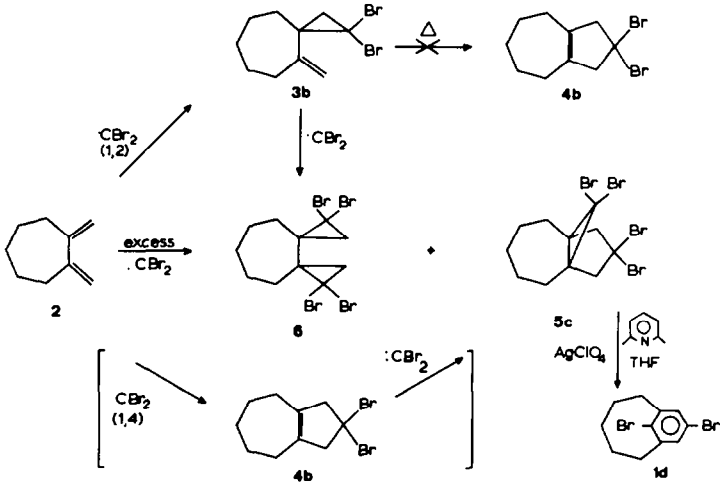
SYNTHESIS OF 8,11-DIHALO[5]METACYCLOPHANES (1b-d)

Following the accidental discovery of 1a and inspired by a rationalization of its formation,[1a] we have developed a systematic synthesis of 1a[1b] and, in particular, of 1b[1d] (Scheme 1).

Scheme 1



Scheme 2



In all cases, 1,2-dimethylenecycloheptane (2)[6] served as a starting material. By addition of dichlorocarbene, 2 was converted to 3a which by flow pyrolysis[1d] or, preferentially, by flash vacuum thermolysis (FVT) was rearranged to 4a. A second dichlorocarbene addition to 4a yielded the tetrachloropropellane 5a. Partial reduction of 5a with triphenyltin hydride followed by elimination of hydrogen chloride with potassium t-butoxide in dimethylsulfoxide gave 1a.[1b] This mode of elimination was not applicable to 5a, but aromatization of 5a was achieved with silver perchlorate and 2,6-lutidine[7] in tetrahydrofuran at room temperature and gave 1b in 70% yield.

For the synthesis of 1c, the same strategy could be followed as for 1b with the obvious difference that dibromocarbene was added to 4a; 5b was isolated in 60% yield (Scheme 1). Treatment of 5b with silver perchlorate and 2,6-lutidine in tetrahydro-

furan at room temperature afforded 1c which, after column chromatography, was isolated in 40% yield. The rate of formation of 1c was comparable to that of 1b (ca. 20 h), presumably because the silver ion induced elimination of hydrogen chloride in the five-membered ring is the rate-determining step in both cases. The reason for the drop in yield (1b: 70%; 1c: 40%) is less obvious; lower yields were also observed in the formation of 1d (40%, vide infra) and thus must be related to the aromatization step, which apparently gives more byproducts when bromide ion is the leaving group.

The synthesis of 1d was achieved, in principle, via the same synthetic approach, although for a trivial practical reason, the experimental execution was in part different (Scheme 2). The practical difficulty we encountered was that after the 1,2-addition of dibromocarbene to 2, which affords 3b, the envisaged thermal vinylcyclopropyl rearrangement of 3b to 4b did not succeed under a variety of conditions; only dark polymers were obtained, and their formation was accompanied by the evolution of hydrogen bromide. Probably, 4b was not stable under the reaction conditions.

Fortunately, we discovered an alternative approach to the desired 5c. Under the conditions of Makosza,[7] the addition of dibromocarbene to 2 afforded 5c directly in 14% yield; the double 1,2-adduct 6 was expectedly the main product (56% yield). It is highly probable that the formation of 5c proceeds by a 1,4-addition of dibromocarbene to 2, yielding 4b, which adds a second dibromocarbene to give 5c. Such 1,4-additions of carbenes to dienes are extremely rare; the only precedent has recently been observed in the analogous addition of dichlorocarbene to 2, which gave 0.6% 4a.[8] We are presently engaged in a systematic investigation of 1,4-additions of carbenes and therefore wish to postpone a more detailed discussion on this matter; it should be pointed out, however, that the formation of 14% of 5c requires the formation of at least 14% 4b from 2, which is an extremely high yield for a hitherto nearly non-existent type of reaction.

Low as the yield of 14% 5c may appear from a preparative point of view, it opens at present the only access to 1d. This compound was formed in analogy to the other dihalo[5]metacyclophanes by treatment of 5c with silver perchlorate and 2,6-lutidine in tetrahydrofuran. The reaction was more rapid (4 h at room temperature) than that of 5a and 5b (both 20h at room temperature); again, this can be explained by assuming that the elimination of the first mole of hydrogen halide is the rate determining step for the overall reaction, as hydrogen bromide (5c) is expected to be eliminated faster than hydrogen chloride (5a, 5b).

The structural identification of 1b, 1c and 1d is based on their spectral properties, in particular on the characteristic ^{1}H-NMR spectra, which will be discussed in detail in the next section. The ^{1}H-NMR spectra of the three compounds are very similar, which is important because the structure of 1b has been confirmed by X-ray crystal structure determination.[1f] The UV spectra reflect the strain in the aromatic ring by showing a bathochromic shift in comparison with the corresponding dihalo-m-xylenes (Table 1).

CONFORMATIONAL ANALYSIS OF THE PENTAMETHYLENE BRIDGES OF 1b-d

According to the X-ray crystal structure determination,[1f] 1b has a boat-shaped benzene ring (see Introduction) and a quasi-crown conformation of the eight-membered ring which is formed by the pentamethylene bridge and the three bow atoms of the aromatic ring (Fig. 1, A); the molecule has C_s symmetry. At low temperature (below 263K), the ^{1}H-NMR spectra of 1a and those of the main conformer A of 1b-d are very similar (Fig.2) and also exhibit C_s symmetry, which is also reflected in the ^{13}C-NMR spectra. In contrast to 1a, the ^{1}H-NMR spectra of 1b-d reveal the presence of a second conformer B (Fig. 1) in minor quantities. That A and B are indeed two conformers of the same compound was established by the observation of coalescence at 398K for 1b,[1d] but more convincingly and accurately by spin saturation transfer.[11]

Table 1. UV Spectra of [5]metacyclophanes (1) and the corresponding m-xylenes [a]

Compound	λ_{max} [nm] (log ε)	2-X-5-Y-m-xylene	λ_{max} [nm] (log ε)
1a[b]	306.5 (?)	X = Y = H[e]	272.5 (2.47) 268.5 (2.39) 265 (2.52)
1b[c]	332 (2.30) 272 (3.70) 238 (4.20)	X = Y = Cl[f]	277 (2.16, sh) 270 (2.31) 262 (2.26, sh)
1c[d]	330 (2.30) 277 (3.5) 270 (3.6)	X = Br; Y = Cl[f]	 270 (2.84, sh) 259.5 (2.88)
1d[d]	336 (2.30) 286 (3.50) 243 (3.9)	X = Y = Br[f]	277 (2.17, sh) 268 (2.43) 226 (4.1)

[a] In cyclohexane. [b] Ref.[1a], [c] Ref.[1d], [d] This work, [e] Ref. [9], [f] Ref. [10].

The chemical shifts and coupling constants of the protons in the major conformer A could be assigned unambiguously by decoupling experiments and spectrum simulation (Table 2). Compound 1b was measured in $CDCl_3$ and toluene-d_8. While some chemical shift values showed a strong solvent dependance, the coupling constants are completely identical. Apparently, specific solvation occurs but does not influence the conformation of the highly strained and rigid pentamethylene bridge. As all chemical shifts are shifted to higher field in toluene-d_8, one may assume that the aromatic solvent is preferentially oriented parallel to the plane roughly defined by the benzene ring and the pentamethylene bridge, thereby "sandwiching" 1b. It is noteworthy that the upfield shifts are clearly larger for the five "upper" hydrogens H (X, 1) compared to five "lower" hydrogens H(X,2) (X = 1,2,3), and furthermore larger for H(1.1) and H(2.1) than for H(3.1). This may be explained by specific orientation of toluene somewhat closer to the benzene ring of 1b and on the top of the pentamethylene bridge (Fig.1), opposite to Cl(11). Probably (electronic) interactions between the aromatic rings of the solvent and of 1b as well as steric repulsion of the solvent by Cl(11) are responsible for this orientation of the solvent.

A comparison between 1a and 1b in $CDCl_3$ reveals that H(1.2) ($\Delta\delta$ = 0.82 ppm) and H(3.2) ($\Delta\delta$ = 0.7 ppm) experience a strong downfield shift in 1b. The chemical shifts of these protons in toluene-d_8 are practically the same for 1b, 1c and 1b, so that one may conclude that this downfield shift is typical for all three [5]metacyclophanes bearing a halogen substituents at C(11). It is probably caused by the short distance between halogen and protons; e.g. for 1b, this distance is shorter [H(1.2) - Cl(11): 2.67 Å; H(3.2) - Cl(11): 2.62 Å, respectively; cf. Table 3] than the sum of the Van der Waals radii of H and Cl (r(H...Cl) = 3.55 Å).

Inspection of Table 2 also reveals that both chemical shifts and coupling constants are extremely similar for 1b-d. Consequently both the conformations of the pentamethylene bridged and the nonbonded interactions to Cl(11) and Br(11) are practically the same.

Next we turn to a discussion of the minor conformer B of 1b-d, respectively. The correspondence of its protons signals with those of conformer A was derived from spin saturation transfer. The chemical shifts of H(1.1) and H(2.1) in B were difficult to assign

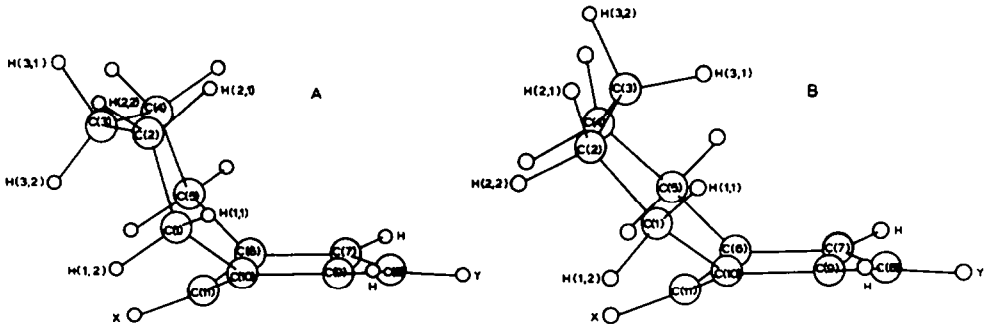


Fig. 1. Pluto drawing and numbering of the conformations A and B of 1b (X = Y = Cl), 1c (X = Br, Y = Cl) and 1d (X = Y = Br). The drawings are taken from MNDO-calculations on 1b[1e]. (Note that the numbering of the hydrogen atoms is different from that used in ref. [1e]).

Table 2. ^{1}H-NMR Data of conformer A of 1a-d[a]

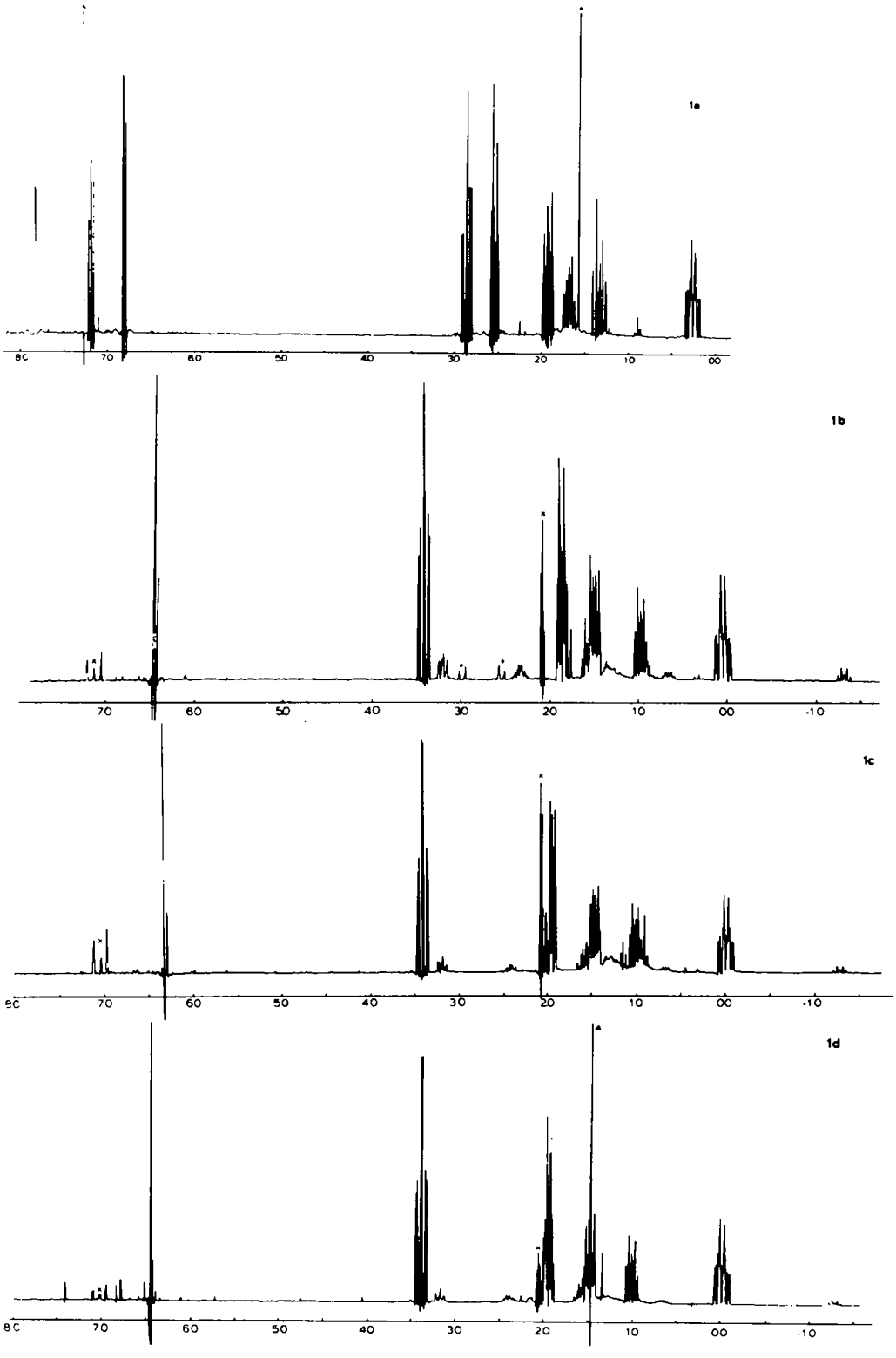
	1a[b]	1b[b]	1b[c]	1c[c]	1d[c]
			δ[ppm]		
H(1.1)	2.54	2.47	1.85	1.93	1.94
H(1.2)	2.85	3.67	3.39	3.40	3.38
H(2.1)	0.25	0.46	0.04	-0.02	0.02
H(2.2)	1.92	1.99	1.48	1.46	1.47
H(3.1)	1.67	1.40	0.97	1.00	1.01
H(3.2)	1.33	2.03	1.82	1.97	1.96
			J[Hz]		
H(1.1)H(1.2)	12.5	12.8	12.8	12.6	12.7
H(1.1)H(2.2)	3.3	3.2	3.2	3.1	3.5
H(1.1)H(2.1)	3.3	3.2	3.2	3.1	3.8
H(1.2)H(2.2)	3.0	3.1	3.1	3.2	3.0
H(1.2)H(2.1)	12.3	12.7	12.7	12.6	12.5
H(2.2)H(2.1)	14.4	14.7	14.7	14.7	14.8
H(2.2)H(3.1)	7.7	8.0	8.0	8.6	7.7
H(2.2)H(3.2)	d	d	d	d	d
H(2.1)H(3.1)	1.1	d	d	d	d
H(2.1)H(3.2)	10.6	10.7	10.7	10.7	10.5
H(3.1)H(3.2)	16.2	16.9	16.9	16.4	16.8

[a] Spectra measured at 250 MHz and 226K; accuracy estimated to be ca. 0.4 Hz; for numbering, see Fig.1; because of the C_s symmetry, the data for H(4.1), H(4.2), H(5.1) and H(5.2) are identical to those of H(2.1), H(2.2), H(1.1) and H(1.2), respectively; [b] $CDCl_3$; [c] Toluene-d_8; [d] Too small to be resolved.
δ[ppm] of aryl protons; 1b 6.45; 1c 6.35; 1d 6.45.

accurately because they were concealed by the signal of H(2.2) of A, but they could be determined by subtracting the spin saturation spectra for these protons from the normal spectra (at 226 K). In this way, all ^{1}H-NMR parameters of 1b-d could be assigned with confidence (Table 4).

As pointed out in our preliminary communication[1e], some spectacular differences are observed between the spectra of conformers A and B for 1b; this trend is now confirmed for 1c and 1d. In going from A to B, the largest shift (Δδ = -2.29 ppm for 1b) is observed for H(3.1) which moves from a normal (or slightly unshielded) position into the shielding cone of the benzene ring; this, incidentally, illustrates that the aromaticity of this ring is essentially intact, in accordance with X-ray data.[1f] To a lesser degree, for 1b H(1.1) (Δδ = -0.29 ppm) and H(3.2) (Δδ = -1.17 ppm) are shifted upfield; for the latter proton, not only shielding by the benzene ring is involved, but also a certain release of

Fig.2: ^{1}H NMR spectra of 1a-d [a]



[a] Measured at 250 MHz and 226K; 1a in $CDCl_3$; 1b-d in toluene-d_8.
Solvent signals are marked by ×; water by Δ; impurity in 1b by o.

Table 3. Nonbonded distances of hydrogen atoms to Cl(11) in 1b

hydrogen	d(H, Cl) [Å]		
	conformer A[a]	Conformer A[b]	conformer B[b]
H(1.1)	3.97	4.28	4.32
H(1.2)	2.67	2.92	3.11
H(2.1)	4.25	4.65	4.52
H(2.2)	4.25	4.55	3.09
H(3.1)	4.12	4.47	4.84
H(3.2)	2.62	2.77	4.36

[a] From X-ray structure[1f]. [b] From MNDO-calculations[1e].

Table 4. ^{1}H-NMR Data of conformer B of 1b-d[a]

	1b	1c	1d
		δ[ppm]	
H(1.1)	1.56	1.56	1.56
H(1.2)	3.18	3.17	3.16
H(2.1)	1.48	1.54	1.54
H(2.2)	2.31	2.41	2.40
H(3.1)	-1.32	-1.30	-1.30
H(3.2)	0.65	0.66	0.66
		J[Hz]	
H(1.1)H(1.2)	12.8	12.8	12.8
H(1.1)H(2.2)	7.0	7.0	7.0
H(1.1)H(2.1)	7.0	7.0	7.0
H(1.2)H(2.2)	10.3	9.5	9.5
H(1.2)H(2.1)	[b]	[b]	[b]
H(2.2)H(2.1)	10.4	10.4	10.4
H(2.2)H(3.1)	[b]	[b]	[b]
H(2.2)H(3.2)	7.7	8.0	7.7
H(2.1)H(3.1)	9.3	9.3	9.5
H(2.1)H(3.2)	[b]	[b]	[b]
H(3.1)H(3.2)	15.9	15.9	15.9

[a] Spectra measured at 250 MHz and 226K in toluene-d_8; accuracy estimated to be ca. 0.4 Hz; for numbering, see Fig. 1; because of the C_s symmetry, the data for H(4.1), H(4.2), H(5.1) and H(5.2) are identical to those of H(2.1), H(2.2), H(1.1) and H(1.2), respectively; [b] Too small to be resolved. The aromatic protons were not observable; they probably coincide with those of conformer A.

of steric compression, as the nonbonded distance to Cl(11) is removed (see Table 3; in A: H(3.2) - Cl(11) 2.77 Å; in B: H(3.2) - Cl(11) 4.36 Å). On the other hand, for H(2.1) (Δδ = +1.44 ppm) and H(2.2) (Δδ = +0.83 ppm) a downfield shift is observed; both move into a less shielded position in conformer B, although for H(2.2), an increase of compression against Cl(11) (in A H(2.2) - Cl(11): 4.55 Å; in B H(2.2) - Cl(11): 3.09 Å) may play a role too. As already noted for conformer A, the chemical shifts and coupling constants are practically identical for 1b-d, so that the conformation of the bridge is also practically the same in B.

Finally, the data of Table 2 and 4 reveal that for both conformers of 1b, there is a very good fit for a Karplus equation[12] between coupling constants ^{3}J(HH) and the dihedral angles Θ of the bridge. For conformer A, the NMR-data were fitted by regression analysis to those of the X-ray structure determination,[1f] resulting in the equation $^3J(HH) = 6.2\ (\pm 0.3) - 0.4\ (\pm 0.6) \cdot \cos\Theta + 5.5\ (\pm 0.7) \cdot \cos^2\Theta$. Similarly, experimental couplings of conformers A and B, on fitting to the data of the MNDO calcula-

tions,[1e] yield the relation $^3J(HH) = 5.5\ (\pm 0.6) - 0.3\ (\pm 0.6)\cdot\cos\theta + 5.6\ (\pm 0.1)\cdot\cos^2\theta$. Both equations lead to practically the same curve which falls into the normal range of Karplus curves. The considerable differences in C-C-C bond angles (at C(1) : 104.7(2)°; at C(2): 121.9(2)°, at C(3): 122.2(2)° [1f]) thus have little influence on $^3J(HH)$.

THE EQUILIBRIUM BETWEEN CONFORMERS A AND B OF 1b-d

As pointed out above, 1a occurs exclusively in conformation A within the limits of detection of ^{1}H-NMR spectroscopy, while 1b-d consist of two conformers A and B which are in a dynamic equilibrium, as evidenced by coalescence[1e] and by spin saturation transfer. The position of this equilibrium could be determined in the temperature range of 223 - 263 K from the ^{1}H-NMR integral ratios (Table 5); within experimental accuracy, the equilibria for 1b-d were found to be temperature independent.

At higher temperatures, the equilibrium ratios could not be deduced directly from the NMR spectra because of line broadening due to coalescence. Somewhat disturbing was the observation that after coalescence, the coalesced chemical shifts for some of the protons (H(1.1), H(1.2) and H(2.2)) were not at the positions calculated with the assumption that the position of the equilibrium was constant also at higher temperatures; the deviations were $\Delta\delta$ = 0.01 - 0.02 ppm. Most of the other protons had coalesced chemical shifts exactly at the calculated positions. A similar problem arose when the high temperature spectra (T > 296 K) were calculated by total line shape analysis[13]. Although the line shapes for H(1.1), H(1.2), H(2.2) and H(3.1) could be perfectly reproduced only with the assumption of a temperature independent ratio of A and B, the positions of H(1.1), H(1.2), and H(2.2) (T = 296 K : δ = 1.81, 3.26 and 1.59 ppm, respectively) did not coincide with the experimental ones (T = 296 K : δ = 1.89, 3.38 and 1.69 ppm, respectively). We have considered two possible explanations for these deviations. The first one, temperature dependant conformational changes at higher temperatures, can be excluded because they would affect coupling constants and hence also line shapes. This was not observed, but it should be kept in mind that very minor conformational changes may not always be detectable by this criterium. The second plausible cause for chemical shift deviations are changes in solvation occurring at higher temperatures. Experimental support for this rationalisation was obtained by measuring the temperature dependance of the ^{1}H-NMR spectra in another solvent, i.e. $CDCl_3$, instead of toluene-d_8. Again, total line shape analysis showed some deviations between calculated and experimental chemical shifts above 296 K; still, an excellent fit of the line shapes was achieved, but only if it was assumed that the position of the equilibrium remained unchanged. The magnitude of the deviations was, however, smaller in $CDCl_3$ than in toluene-d_8; this is expected if changes in solvation are responsible, because the asymmetry of $CDCl_3$ in shape and in magnetic susceptibility is smaller than that of toluene. We therefore feel confident that the position of the equilibrium between conformers A and B is indeed temperature independent in the total investigated range from 223 to 353 K.

Table 5. Equilibrium ratios and thermodynamic parameters for conformers A and B of 1 at 223 - 353 K[a]

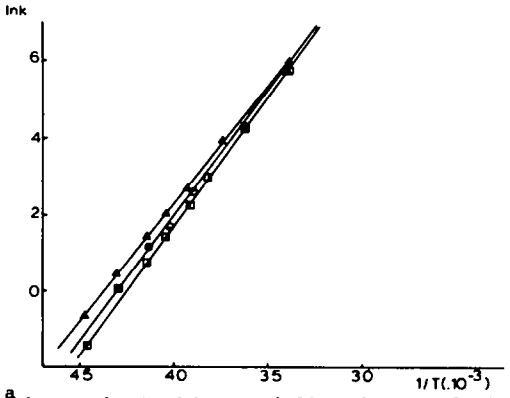
Compound	mole fraction A	mole fraction B	$\Delta\Delta$ H(A,B) [kcal.mol^{-1}]	$\Delta\Delta$ S(A,B) [cal.mol^{-1} degree^{-1}]
1b	0.85	0.15	0	-2.0
1c	0.89	0.11	0	-4.0
1d	0.88	0.12	0	-4.0

[a] Determined from ^{1}H-NMR integral ratios for the range 223 - 263 K and from total line shape analyses for the range 223 - 353 K (see text).

From the (temperature independent) equilibrium ratios of Table 5, one can deduce the thermodynamic equilibrium parameters $\Delta\Delta H(A,B) = 0$ kcal.mol^{-1} and $\Delta\Delta S(A,B) = -2$ (1b) to -4 (1c,1d) cal.mol^{-1}·degree^{-1}. For 1b, this result is within the limits of accuracy in agreement with previously determined values ($\Delta\Delta H(A,B) = 0.7$ kcal.mol^{-1}, $\Delta\Delta S(A,B) = -0.5$ cal.mol^{-1}·degree^{-1}),[1e] but the new values are much more reliable because they were determined by a more accurate method and over a large temperature range. For all three the compounds it thus appears that both conformers have the same enthalpy of formation and that the higher stability of conformer A is due only to a more favourable entropy; presumably, the pentamethylene chain in B is more rigid. It is interesting that the (near) equality of $\Delta\Delta H(A,B)$ for 1b was quite reliably reproduced by the MNDO calculations ($\Delta\Delta H(A,B) = 0.4$ kcal.mol^{-1}).[1e]

The total line shape analysis also afforded the rate constants for the equilibrium A $\rightleftarrows$ B of 1b-d, and from the Arrhenius plots (Fig. 3), the activation parameters were derived (Table 6).

Fig.3. Arrhenius plots for the equilibria A $\rightleftarrows$ B for 1b-d [a]



[a] k Was obtained by total line shape analysis. 1b: Δ (corr.coeff.0.9997); 1c: □ (corr.coeff. 0.9989; 1d: ○ (corr.coeff.0.9996).

The experimental activation enthalpy of 1b ($\Delta H^{\ddagger} = 11.6$ kcal.mol^{-1}) is much smaller than the one which was previously tentatively calculated by the MNDO method ($\Delta H^{\ddagger} = 19.0$ kcal.mol^{-1}).[1e] However, for reasons of economy, the calculations were rather crude in the sense that only a few points on the trajectory were calculated and, which is probably more serious, C_s symmetry was imposed on the molecule throughout the conformational change; apparently, these assumptions were not in line with reality.

DISCUSSION

As the pentamethylene bridges of 1 form part of an eight-membered ring, it seems attractive to discuss the conformations of A and B against the background of the conformational analysis of other eight-membered ring systems, which have received considerable attention in the literature.[14] However, it turns out that it is not easy to find an adequate model for A and B. Taking a Kékulé structure of a [5]metacyclophane (1) as a starting point, 1 may be regarded as a derivative of a (3-methylene-)trans-cyclooctene; this analogy is, however, not satisfactory simply because trans-cyclooctene has a twist conformation[15] in contrast to the C_s geometry of A and B. Disregarding the unsaturation present in A and B, the chair-chair (A) and the boat-chair (B) conformations of cyclooctane come to mind as reasonable models. In view of the subtle balance between these two conformations in cyclooctane itself[14], it is not to be expected that a simple qualitative analysis will be meaningful. According to the X-ray structure of 1b[1f] and to MNDO calculations (1a and 1b)[1e], A has a more or less staggered conformation, whereas B (only MNDO available[1e]) shows considerable eclipsing of

Table 6. Activation parameters for the conversion of conformer A into conformer B of 1b-d

	$\Delta G^{\ddagger}$ [a] [kcal.mol^{-1}]	$\Delta H^{\ddagger}$ [kcal.mol^{-1}]	$\Delta S^{\ddagger}$ [cal.mol^{-1}·degree^{-1}]
1b	13.2	11.6	-5.5
1c	13.4	12.3	-3.6
1d	13.4	12.2	-3.9

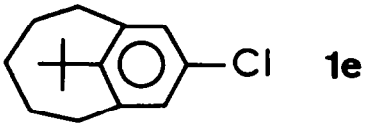
[a] At T = 296 K.

the bridge. We feel that it is largely due to this difference that in the unsubstituted parent compound 1a we find a clear preference of A over B. The experimental result that B is not observed at all can be rationalized by the following estimate. We assume for 1a $\Delta\Delta H(A,B) = 1.2$ kcal.mol^{-1} (the value derived from the MNDO calculation[1e]) and for $\Delta\Delta S(A,B) = -3$ cal.mol^{-1}·degree^{-1} (mean value of 1b and 1c); this leads to a ratio A:B = 97:3 (296 K) which is about the detection limit of ^{1}H NMR spectroscopy. Simple intuition, and inspection of the nonbonding interactions in models of conformer A of 1b suggest that the replacement of H(11) (1a) by Cl(11) (1b) will decrease the stability of A relative to B, particularly because of the strong nonbonding interaction between H(3.2) and Cl(11) (Fig. 1 and Table 3; H(3.2)-Cl(11): 2.77 Å; sum of the Van der Waals radii: 3.55 Å[16]). The MNDO calculations correctly predicted this trend by yielding a smaller $\Delta\Delta H(A,B) = 0.4$ kcal.mol^{-1} for 1b which is close to the experimental value of $\Delta\Delta H(A,B) = 0$ kcal.mol^{-1}.

However, the situation is not quite so simple. In the first place, the trend for $\Delta\Delta H(A,B)$ does not continue when replacing Cl(11) in 1b by the even larger Br(11) in 1c and 1d. Furthermore, a closer inspection of Table 3 reveals that while the nonbonding interaction between H(3.2) and Cl(11) is probably the most serious one in A and is completely relieved on going to B, there are other nonbonding interactions which are nearly as severe (H(1.2)-Cl(11) is 2.92 Å in A and 3.11 Å in B, respectively) or, on the contrary, are introduced in B and are in fact quite unfavourable: H(2.2)-Cl(11) is 3.09 Å in B! ; the latter is even more important because actually two hydrogens (H(2.2) and H(4.2)) are involved. With increasing size of the substituent at C(11), this effect is expected to destabilize B and to counteract the relief of strain obtained by removing H(3.2). It should be pointed out, however, that the differences in interactions, important as they are for the enthalpy of 1, do not appear to have a strong influence on the conformation of the bridge as such. This is evidenced by the great similarity of the ^{1}H NMR spectra; in view of the rich detail of these spectra, this evidence is particularly compelling.

When replacing chlorine (1b) by bromine (1c,1d) the steric effect levels off. This is at first sight unexpected, because bromine has a larger Van der Waals radius.[16] However, conformational size is apparently not a constant entity, but depends on the direction and on the polarisability of the group. Both in the conformational preferences of halogen-substituted cyclohexanes[17] and in the rotational barriers of halogen-substituted ethanes,[18] increasing interactions are observed in going from fluorine to chlorine, but the increment becomes smaller from chlorine to bromine and is more or less absent from bromine to iodine. It appears as if the heavier halogens have a pear-shaped rather than a symmetrical radial arrangement of their electron clouds; they will also yield to steric compression more readily because they are more polarisable.

A more detailed knowledge of the geometries of 1c and 1d is required to explain the slight reversal in stability in favour of conformer A in 1c and 1d. One factor may be the more asymmetric shape and higher polarisability of Br(11). On the other hand, it is important to point out that 11-t-butyl-8-chloro[5]metacyclophane 1e[19] has the much bulkier t-butyl group in position 11; nevertheless, only conformation A is observed. Preliminary MNDO calculations[10] suggest that in 1e, nonbonded interactions are practically identical for A and B, so that the differences in stability are caused by the inherent conformational energies of the bridges. In fact, $\Delta\Delta H(A,B)$ is calculated to be approximately 1 kcal.mol^{-1} in favour of A which, by a similar estimate as presented for 1a, would explain why conformer B escapes detection by ^{1}H NMR spectroscopy.



1e

The activation parameters (Table 6) for the inversion from the "chair-chair" conformation A to the "boat-chair" conformation B are slightly higher than those for the chair-boat barrier in cyclohexane ($\Delta H^{\ddagger}$ = 10.8 kcal.mol^{-1})[20], but considerably higher than those for cyclooctane ($\Delta H^{\ddagger}$ = 7.4 kcal.mol^{-1})[21]. Undoubtedly, the strain in the pentamethylene bridge removes many degrees of freedom which are available in the more flexible cyclooctane ring and permit the latter to find a lower energy pathway. The barrier depends only slightly on the nature of the halogen substituent at C(11). In view of the uncertainties which remain in the conformational analysis of A and B, it would be premature to comment on the experimental result that the activation enthalpies for the conversion A ⇄ B (Table 6) is slightly higher for 1c and 1d. It is, however, of interest that the slightly negative activation entropies are of the same order of magnitude as the reaction entropies, especially for 1c and 1d. Apparently, the higher rigidity of conformer B is largely realized already in the transition state.

CONCLUSION

The three 8,11-dihalo[5]metacyclophanes 1b, 1c and 1b occur in two conformers A and B. A detailed analysis of their ^{1}H NMR spectra defined the conformations of the pentamethylene bridged of A and B which were found to be practically identical for the three compounds and are in good agreement with MNDO calculations. The chair-chair type conformer A is slightly more stable than the chair-boat conformer B. This is mainly due to lesser torsional strain in A, but transannular nonbonding interactions, which vary with the substituent at C(11), and entropy effects determine the exact position of the dynamic equilibrium between A and B in a subtle interplay.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WH-250 spectrometer at a frequency of 250 MHz, unless otherwise stated. The spectrometer was field frequency locked on the deuterium resonance of the solvent (either toluene-d_8 or $CDCl_3$). The sample temperature was regulated with a Bruker B-VT 1000 temperature control unit. It was checked in the probehead with a copper constantane thermocouple. If necessary, a Lorentz Gauss transformation was carried out before Fourier transformation, yielding Gaussian enhanced spectra. All spectra were analyzed by standard iterative simulation techniques using the LAOCOON III like PANIC program (Bruker). Total line shape analysis was performed on a Cyber computer using the DNMR program, developed by G. Binsch[11,13] The program was placed at our disposal by the NMR program Library, Daresbury Laboratory.
All products were analyzed by GCMS, using a Finnigan-4000 mass spectrometer; exact mass measurement was performed with a Varian CH-5 DF mass spectrometer at an ionization potential of 70 eV.
Ultra violet spectra were recorded on a Cary 114 spectrophotometer. All melting points are uncorrected.
Micro analysis were performed by the Instituut voor Toegepaste Chemie TNO, Zeist, The Netherlands, under the supervision of Mr. G.J. Rotscheid.

9,9,11,11-Tetrachlorotricyclo[5.3.1.0^{1,7}]undecane (5a) and 11,11-dibromo-9,9-dichlorotricyclo[5.3.1.0^{1,7}]undecane (5b)

To a mixture of 9,9-dichloro[5.3.0]dec-1(7)-ene[1b] (4a, 6.2 g, 0.03 mol), $CHCl_3$ or $CHBr_3$, respectively, (0.24 mol), cetyltrimethylammonium bromide (0.68 g, 1.9 mmol) and two drops of ethanol, a solution of NaOH (9.6 g, 0.24 mol in water (10 ml) was added within 15 min. under vigorous stirring. The stirring was continued for 18 h at room temperature and 2 h at 45°C. After cooling to room temperature, water (200 ml) was added, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with water, dilute HCl (1N) and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was a pale yellow solid and was purified by recrystallization from ethanol.
5a: yield 6.86 g (0.024 mol, 80%) after recrystallization; m.p. = 117°C. ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.26, 3.14 (AB system, J_{AB} = 16 Hz, 4H), 2.20-1.20 (m, 10H). Mass spectrum m/z (rel. intensity): 286(9) [5a]$^{+\cdot}$ with isotope pattern, 232(100). HRMS Calc. [$C_{11}H_{14}{}^{35}Cl_4$]$^{+\cdot}$: 285.9849. Found: 285.9839.
5b: yield 7.1 g (0.019 mol, 62%) after recrystallization; m.p. = 117°C. ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.22 (bs, 4H), 2.3-1.7 (m, 10H). Mass spectrum m/z (rel. intensity): 374(15.8), 376(46), 378(40), 380(12.1)[5b]$^{+\cdot}$ with isotope pattern, 320(100). HRMS Calc. ($C_{11}H_{14}{}^{79}Br_2{}^{35}Cl_2$): 376.9456. Found: 376.9416. Found: C,35.50; H,3.80; Br,41.70; Cl,19.00. $C_{11}H_{14}Br_2Cl_2$ (M = 376.96) requires: C,35.05; H,3.74; Br,42.40; Cl,18.81.

9,9,11,11-Tetrabromotricyclo[5.3.1.0^{1,7}]undecane (5c)

To a mixture of 1,2-dimethylenecycloheptane[6] 2, 3.66 g, 0.03 mol), $CHBr_3$ (0.24 mol), trimethylammonium bromide (0.68 g, 1.9 mmol) and two drops of ethanol, a solution of NaOH 9.6 g, 0.24 mol) in water (10 ml) was added within 15 min. under vigorous stirring. The stirring was continued for 18h. at room temperature and 2 h. at 45°C. After cooling to room temperature, water (200 ml) was added, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with water, dilute HCl (1N) and brine, dried ($MgSO_4$) and concentrated under reduced pres-

sure. The residue was a viscous oil. Compound 5c was obtained from the residue by fractional crystallization from acetone at -20°C. The mother liquor was evaporated to dryness; the residue consisted of practically pure 2,2,5,5-tetrabromodispiro[2,0,2,5]undecane (6), which was recrystallized from methanol.
5c: yield 1.94 g (4.2 mmol, 14%); m.p. = 118°C. ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.51 (s, 4H), 1.6-2.3 (m, 10H) m/z (rel. intensity); 462(4.6), 464(18.3), 466(28.7), 468(16.5), 470(4.1). $[5c]^{+\cdot}$ with isotope pattern, 305(100). HRMS. Calc. ($C_{11}H_{14}{}^{79}Br_3{}^{81}Br$): 463.7812. Found: 463.7811. Found C,28.47; H,3.07; Br,68.86. $C_{11}H_{14}Br_4$ (M = 465.87) requires: C,28.36; H,3.03; Br,68.61.
6[22]: yield 7.80 g (16.8 mmol, 56%); m.p. = 124°C. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.6-2.2 (m, 10H), 1.56-1.40 (AB system, J_{AB} = 14 Hz, 4H). HRMS Calc. ($C_{11}H_{14}{}^{79}Br_2{}^{81}Br_2$): 465.7785. Found: 465.7788.

8,11-Dihalo[5]metacyclophanes (1b,c,d); general procedure

To a mixture of $AgClO_4$ (1.24 g, 6 mmol), 2,6 lutidine (0.37 g, 3.4 mmol) in dry THF (6 ml), a solution of 5a, 5b or 5c (1.5 mmol, respectively in dry THF (3 ml) was added in 5 min. under stirring. After stirring for several hours (5a,5b : 20 h.; 5c: 4 h.) at room temperature, the reaction mixture was filtered of through a glass filter. The filtrate was evaporated and the residue was purified by column chromatography (silicagel, n-pentane).
1b: yield 0.22 g (1.05 mmol, 70%); m.p. = 42°C. Mass spectrum m/z (rel. intensity); 214(34)[1e]; $[1b]^{+\cdot}$, 179(100), HRMS. Calc. ($C_{11}H_{12}{}^{35}Cl_2)^{+\cdot}$: 214.0316. Found: 214.0322.
1c: yield 0.15 g (0.6 mmol, 40%); m.p. = 25 - 30°C, waxy solid. Mass spectrum m/z (rel. intensity): 258(41), 260(82), 262(22.4) $[1c]^{+\cdot}$ with isotope pattern, 144(100). HRMS. Calc. ($C_{11}H_{12}{}^{79}Br{}^{35}Cl)^{+\cdot}$: 257.9811. Found: 257.9807.
1d: yield 0.18 g (0.6 mmol, 40%); m.p. = 37°C. Mass spectrum m/z (rel. intensity): 302(1), 304(2), 306(0.6) $[1d]^{+\cdot}$ with isotope pattern, 129(100), HRMS. Calc. ($C_{11}H_{12}{}^{79}Br_2)^{+\cdot}$: 301.9316. Found: 301.9331.

ACKNOWLEDGEMENT.

We thank Mr. J.C. Klamer for experimental contributions, and Prof. P. von R. Schleyer for valuable suggestions concerning conformational substituent effects. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid (L.W.J.) from the Netherlands Organisation for the Advancement of Pure Research (ZWO).

REFERENCES AND NOTES

1. a. J.W. van Straten, W.H. de Wolf and F. Bickelhaupt, Tetrahedron Lett. 4667, (1972);
   b. L.A.M. Turkenburg, P.M.L. Blok, W.H. de Wolf and F. Bickelhaupt, Tetrahedron Lett. 22, 3317 (1981);
   c. L.A.M. Turkenburg, P.M.L. Blok, W.H. de Wolf and F. Bickelhaupt, Angew. Chem. 94, 291 (1982);
   d. L.A.M. Turkenburg, W.H. de Wolf and F. Bickelhaupt, Tetrahedron Lett. 24, 1817 (1983);
   e. L.A.M. Turkenburg, W.H. de Wolf, F. Bickelhaupt, W.P. Cofino and K. Lammertsma, Tetrahedron Lett. 24, 1821 (1983);
   f. L.W. Jenneskens, J.C. Klamer, H.J.R. de Boer, W.H. de Wolf, F. Bickelhaupt and C.H. Stam, Angew. Chem. 96, 236 (1984);
   g. See also the review by S.M. Rosenfeld and K.A. Choe in Cyclophanes, P.M. Keelen and S.M. Rosenfeld, ed., Academic Press, New York, 1983, Vol. I, chapter 5.
2. V.V. Kane, A.D. Wolf and M. Jones, Jr., J. Am. Chem. Soc. 96, 2643 (1974).
3. S.L. Kammula, L.D. Iroff, M. Jones, Jr., J.W. van Straten, W.H. de Wolf and F. Bickelhaupt, J. Am. Chem. Soc. 99, 5815 (1977).
4. a. J. Liebe, C. Wolff and W. Tochtermann, Tetrahedron Lett. 23, 171 (1982);
   b. C. Wolff, J. Liebe and W. Tochtermann, Tetrahedron Lett. 23, 1143 (1982);
   c. J. Liebe, C. Wolff and W. Tochtermann, Tetrahedron Lett. 23, 2439 (1982);
   d. C. Krieger, J. Liebe and W. Tochtermann, Tetrahedron Lett. 24, 707 (1983);
   e. J. Liebe, W. Tochtermann and J. Weiss, Tetrahedron Lett. 24, 2549 (1983).
5. a. Y. Tobe, K. Kakiuchi, Y. Odaira, T. Hosaki, Y. Kai and N. Kasai, J. Am. Chem. Soc. 105, 1376 (1983);
   b. Y. Tobe, K. Ueda, K. Kakiuchi and Y. Odaira, Chemistry Lett. 1645, (1983).
6. J.W. van Straten, J.J. van Norden, T.A.M. van Schaick, G.Th. Franke, W.H. de Wolf and F. Bickelhaupt, Recl. Trav. Chim. Pays-Bas 97, 105 (1978).
7. a. P. Grice and C.B. Reese, Tetrahedron Lett. 2563 (1979);
   b. P. Grice and C.B. Reese, J. Chem. Soc., Chem. Commun. 1980, 424.
8. L.A.M. Turkenburg, W.H. de Wolf and F. Bickelhaupt, Tetrahedron Lett. 23, 769 (1982).
9. Ultraviolet Spectral Data, API Research Project 44, Serial No.56.
10. L.W. Jenneskens, to be published.
11. a. S. Forsen and R.A. Hoffman, J. Chem. Phys. 39, 2892 (1963);
   b. I.D. Campbell, C.M. Dobson, R.G. Radcliffe and R.J.P. Williams, J. Magn. Reson. 29, 397 (1978).
12. H. Günther, NMR Spektroskopie, Georg Thieme Verlag, Stuttgart, 1973, p.113.
13. a. G. Binsch and H. Kessler, Angew. Chem. 92, 445 (1980);
   b. G. Binsch, J. Am. Chem. Soc. 91, 1304 (1969);
   c. G. Binsch and D.A. Kleier, J. Magn. Reson. 3, 146 (1970);
   d. D.J. Loomes, R.K. Harris, P. Anstey and W. Smith, The NMR Program Library, Science Research Council, Daresbury Laboratory, Daresbury, 1979.
14. a. F.L. Anet, Topics in Current Chemistry 45, 169 (1974);
   b. J. Dale, Stereochemistry and Conformational Analysis, Universitetsforlaget, Oslo, 1978, p.195.

15. N.L. Allinger and J.T. Sprague, J. Am. Chem. Soc. 94, 5734 (1972).

16. B. Testa, Principles of Stereochemistry, Marcel Dekker, Inc., New York, 1979.

17. F.R. Jensen, C. Hackett Bushweller and B.H. Beck, J. Am. Chem. Soc. 91, 344 (1969).

18. J.E. Anderson and H. Pearson, Tetrahedron Lett., 2779 (1972).

19. L.W. Jenneskens, J.C. Klamer, W.H. de Wolf and F. Bickelhaupt, J. Chem. Soc., Chem. Commun. 1984, 733.

20. F.A.L. Anet and A.J.R. Bourn, J. Am. Chem. Soc. 89, 760 (1967).

21. F.A.L. Anet and J.S. Hartman, J. Am. Chem. Soc. 85, 1204 (1963).

22. Compound 6 has been (implicitly) described earlier: J.W. van Straten, I.J. Landheer, W.H. de Wolf and F. Bickelhaupt, Tetrahedron Lett. 4499 (1975).