(4-[(p-nitrophenyl)azo]phenol); 0.0092 M, 0.092 M (phenol). The exceptions for the ^1H NMR studies of **4** are listed with use of the same format: 0.015 M, 0.094 M (4-cyanophenol); 0.0075 M, 0.075 M (4-fluorophenol); 0.010 M, 0.050 M (6-nitro-2-naphthol); 0.0075 M, 0.028 M (4-[(p-nitrophenyl)azo]phenol). For all studies, 400 μL of the host solution was used.

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Supplementary Material Available: Tables of X-ray data for **1**, **2**, **4**, and the 1:1 adduct of **4** with Ph_2SnCl_2 including crystal data, collection parameters, solution and refinement data, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen atom coordinates, and isotropic displacement parameters (49 pages); tables of observed and calculated structure factors (121 pages). Ordering information is given on any current masthead page.

Reactivity of 8,11-Dihalo[5]metacyclophanes[1]

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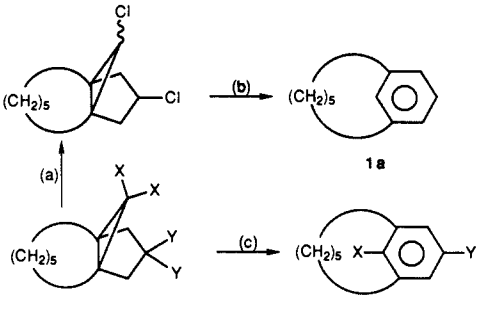
Abstract: The highly bent and strained 8,11-dihalo[5]metacyclophanes **1b–d** were subjected to a variety of reactions in order to compare their behavior with that of normal, planar aromatics. Indeed, a strongly deviating reactivity of **1** was observed. With acid, rapid Wagner–Meerwein rearrangement to the ortho isomers **3** occurred, with partial loss of the substituent at position 11 (between the bridge) to furnish **4**; theoretical calculations show that relief of strain on bridgehead protonation is the initiating step. Irradiation of **1** furnished mainly **3**. This rearrangement was shown by ^{13}C-labeling to proceed via a benzvalene intermediate; a minor side reaction was radical cleavage of the 11-halogen which leads to radical attack at the central methylene group of the bridge and finally to **15**. The transformation **1** → **15** was more efficiently achieved with the complex reducing agent $NaH/Ni(OAc)_2$; in this case, however, removal of the second halogen to **18** and overreduction to **19** also occurred. Similarly, attempted catalytic reductive removal of the halogen was not successful, as the hydrogenation went on to the fully saturated bicyclo[5.3.1]undecane (**16**). The high reactivity of the aromatic nucleus was also apparent from the unusual ease of Diels–Alder reactions under rather mild conditions. Remarkable, too, is the reactivity of **1b–d** toward organolithium reagents. While *n*-butyllithium gave variable results depending on the halogen, *tert*-butyllithium showed either the unusual S_N2-substitution of Cl-11 in **1b** (to give **1e**), the expected double bromine–lithium exchange with **1c** (to give **25**), or a single-electron-transfer reaction with **1d** (to give **15d**). It is concluded that the enhanced and/or unusual reactivity of [5]metacyclophanes is mainly due to relief of strain in the initial stages of these reactions and not (primarily) to reduced aromatic character.

One of the intriguing aspects in the chemistry of short-bridged [*n*]cyclophanes is the question how bending of the benzene ring influences the chemical and physical properties of these highly strained compounds. In contrast to the [*n*]paracyclophanes, which have been studied experimentally[2,3] and theoretically,[4] the [*n*]-metacyclophanes have received less attention.

Although the synthesis of [*n*]metacyclophanes with n = 10, 7, 6,[5] and 5[6] has been reported and the intermediacy of [4]metacyclophane[7] has been invoked, experimental data concerning their reactivity are scarce. Nevertheless, it could be deduced that [*n*]metacyclophanes with $n \leq 7$ possess extraordinary properties.[2b,6b,8,9] This was initially rationalized by invoking the occurrence of bond fixation in the bent benzene ring toward a 1,3,5-cyclohexatriene-like structure.[9a]

However, when crystalline derivatives of the hitherto smallest isolable representative of [5]metacyclophane (**1a**), i.e., 8,11-dihalo[5]metacyclophanes (**1b–d**) became available (Scheme I),[10] an X-ray structure determination of 8,11-dichloro[5]metacyclophane (**1b**) unambiguously showed that despite the large deviations from planarity of the bent benzene ring (e.g., at the bow of the boat, the bending angle is 26.8°), the aromatic carbon–carbon bond lengths were practically uniform and typical for a delocalized aromatic compound (1.393 ± 0.007 Å).[11] Obviously, bond fixation cannot be responsible for the extraordinary reactivity of [*n*]metacyclophanes with $n \leq 7$. Consequently,

Scheme I[a]



2a : X = Y = Cl
2b : X = Y = Br
2c : X = Br, Y = Cl

1b : X = Y = Cl
1c : X = Y = Br
1d : X = Br, Y = Cl

[a] (a) **2a** + $2Ph_3SnH$; (b) *t*-BuOK; (c) $AgClO_4$, lutidine, THF.

an explanation was put forward based on a systematic theoretical investigation of [*n*]metacyclophanes with n = 7, 6, 5, and 4.[12a]

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(1) Taken in part from Jenneskens, L. W. Ph.D. Thesis, Vrije Universiteit, Amsterdam, The Netherlands, 1986.

(2) For reviews see: (a) Keehn, P. M.; Rosenfeld, S. M. *Cyclophanes*; Academic Press: New York, 1983. (b) Bickelhaupt, F.; De Wolf, W. H. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 459. (c) Bickelhaupt, F. *Pure Appl. Chem.* **1990**, *62*, 373.

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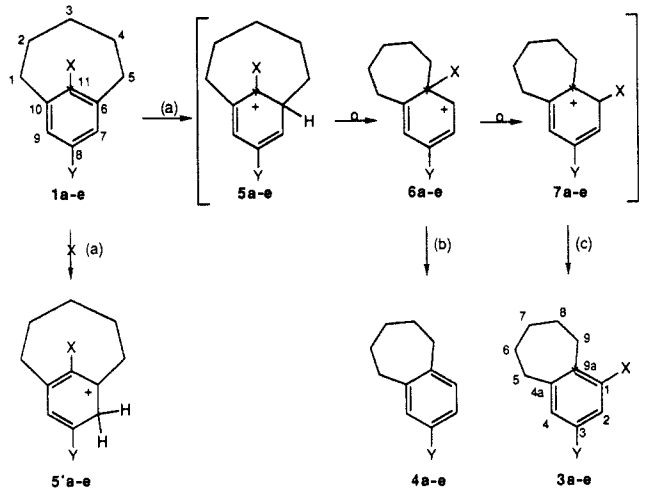
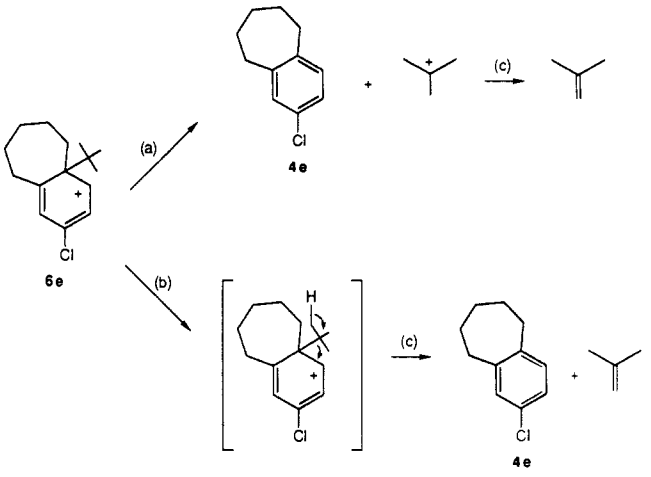
Scheme II[a]



[a] **a**, X = Y = H; **b**, X = Y = Cl; **c**, X = Y = Br; **d**, X = Br, Y = Cl; **e**, X = *t*-Bu, Y = Cl. * = ^{13}C label in **1b** and **3b**. (a) H^+, (b) $-X^+$, (c) $-H^+$.

The results suggested that the increase in strain with decreasing *n* is the dominating factor for the enhancement of reactivity. We have now investigated the chemical behavior of the 8,11-dihalo-[5]metacyclophanes (**1b–d**) under a variety of experimental conditions. A number of unusual rearrangement, addition, and substitution reactions, which find no counterpart in ordinary aromatic chemistry, are reported.

Scheme III[a]



[a] (a) E1, (b) E2, (c) $-H^+$.

Since the 8,11-dihalo[5]metacyclophanes (**1b–d**) are relatively easily accessible in contrast to the parent compound (**1a**),[6] we have also investigated the possibility of opening a better preparative route from **1b,c** to **1a** as an ancillary goal.

Results and Discussion

Acid-Catalyzed Rearrangement of 1a–e. A characteristic reaction of short-bridged [*n*]cyclophanes is the acid-catalyzed rearrangement to their corresponding ortho isomers, the benzocycloalkenes. A tentative investigation of **1a** and **1b** revealed that **1a** rearranged instantaneously and quantitatively to **3a** at ambient temperature with catalytic amounts of acid.[6a] In contrast, the rearrangement of **1b** was considerably slower under similar conditions.[9b] Three hours were needed for complete reaction. Besides **3b**, a side product, identified as **4b**, was found in ca. 30% yield (Scheme II). Similar results were obtained for **1c** and **1d**, which yielded **3c**, **4c** and **3d**, **4d**, respectively, in a ratio of 2:1.

The formation of the rearrangement products was rationalized by the mechanism shown in Scheme II. An analogous mechanism has been proposed for the acid-catalyzed rearrangement of 7,8-benzo-11-chloro[5]metacyclophane.[13] The key step is protonation at one of the bridgehead positions (C(6) or C(10)) to give the primary cationic intermediate **5**. The latter rearranges to **3** via a 1,2-alkyl shift to **6** followed by a 1,2-shift of a halonium ion to **7** and subsequent deprotonation. The formation of the side products **4** from **1b–d** can also be rationalized by the proposed mechanism. Formally, they can be derived by a cationic abstraction of the halogen substituent X from either the intermediate **6** or **7**. In view of the much better nucleofugic properties of the proton compared to the halonium ion, it is likely that the latter is cleaved from **6**. Apparently, this reaction competes efficiently with the 1,2-migration. Presumably, the anion of the trifluoroacetic acid used for the rearrangement acts as the nucleophile which attacks the halogen in an S_N2-type substitution.

A rearrangement with *complete* loss of the substituent X at C(11) was observed for 11-*tert*-butyl-8-chloro[5]metacyclophane (**1e**), which was unexpectedly obtained from **1b** with *tert*-butyllithium at −70 °C (vide infra).[14] On treatment with catalytic amounts of acid, an instantaneous and quantitative rearrangement to **4e** was observed; **3e** could not be detected in the reaction mixture. This suggests that in the case of **1e**, a 1,2-alkyl shift (**6e** → **7e**) of the *tert*-butyl group does not occur. This can be rationalized by the easy elimination of the *tert*-butyl group. It

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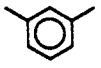
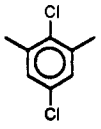
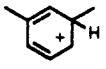
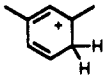
Table I. MNDO Heats of Formation ($\Delta H_f°$) and Proton Affinities (PA)[a]

compd	$\Delta H_f°$	PA[b]
1a	45.6[c]	
1b	34.7[c]	
5a	218.2	194.6
5b	222.7	179.2
5'a	230.3	182.5
5'b	232.7	169.2
	5.9 (4.12)[d]	
	−5.9	
	196.6	176.5
	189.0	184.1
C_2H_6	−19.7[e] (−20.2)[d]	
C_3H_8	−24.9[e] (−24.8)[d]	

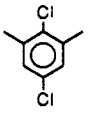
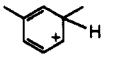
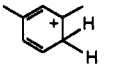
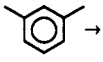
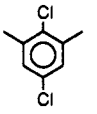
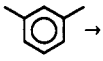
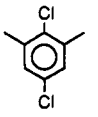
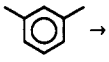
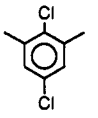
[a] In kcal·mol^{-1}. [b] PA derived from the equation PA = ($\Delta H_f°$(B, MNDO) + $\Delta H_f°$(H^+)) − $\Delta H_f°$(BH^+, MNDO): $\Delta H_f°$(H^+) = 367.2 kcal·mol^{-1}.[16b] [c] Cf. ref 12a. [d] Experimental $\Delta H_f°$.[16c] [e] Cf. ref 16d.

can proceed via an E1-type mechanism giving **4e** and the relatively stable *tert*-butyl cation, which subsequently deprotonates to 2-methylpropene. The latter was detected in the ^{1}H-NMR spectrum in equimolar amounts with respect to **4e**. However, an E2-type mechanism seems equally feasible (Scheme III). The results for **1e** support the assumption that the side products **4** observed on rearrangement of **1b–d** are derived from the intermediate **6** (Scheme II). Although all the experimental results can be rationalized conveniently by the proposed mechanism, none of the cationic intermediates proposed in Scheme II could be characterized directly. Therefore, further support was obtained from the acid-catalyzed rearrangement of [11-^{13}C]**1b** (^{13}C enrichment ca. 10%). The latter was prepared from the appropriately ^{13}C labeled precursor **2a**. It should be noted that the ^{13}C-NMR spectra of [5]metacyclophanes are highly characteristic;[15] in comparison with the *m*-xylenes having the same substitution pattern, a downfield shift of approximately 8 ppm was observed for the aromatic carbon atom C(11). In agreement with the proposed mechanism, the acid-catalyzed rearrangement of [11-^{13}C]**1b** yielded **3b**, the ^{13}C-NMR spectrum of which revealed an enhanced signal at δ = 139.3 ppm for C(9a) (Scheme II).

We have investigated the key step, i.e., protonation of **1a** and **1b**, theoretically. Proton affinities (PA's) for the carbon atoms C(6) and C(7) were calculated by the MNDO method.[16a] For comparison, the corresponding PA's of the unstrained reference compound *m*-xylene were calculated. In the case of **1a** and **1b**, protonation at the bridgehead carbon atom C(6) or C(10) is favored thermodynamically by about 10–12 kcal·mol^{-1}; expectedly, the reverse order is calculated for protonation of *m*-xylene (Table I).[17]

Also informative is an analysis of the homodesmotic[18] reactions presented in Table II. The calculated heats of reaction (ΔH) are either a measure for the strain energy (SE = $-\Delta H$) or a measure for the effect of chlorine substitution. Entries 1 and 2 yield the SE of **1a** and **1b**, respectively, which are in excellent agreement with those calculated with Benson[19] group increments.[12a] Of special interest are the calculated ΔH's of entries 3 and 4. The calculations clearly predict that protonation at C(6) or C(10) (**5a**) leads to a substantial reduction of the strain (ΔSE = 46.0–27.9 = 18.1 kcal·mol^{-1}). In contrast, protonation at C(7) or C(9) (**5'a**) yields SE = 47.6 kcal which is essentially the same as that of unprotonated **1a**. Thus, the driving force for the acid-catalyzed rearrangement is the release of strain realized in protonation, i.e., in the very first step of the reaction sequence. A similar conclusion has been reached by calculations in the [*n*]paracyclophane series.[3r]

Table II. Heats (ΔH) of Homodesmotic Reactions[a]

entry	reaction	ΔH
1	**1a** + 6 C_2H_6 →  + 5 C_3H_8	-46.0
2	**1b** + 6 C_2H_6 →  + 5 C_3H_8	-46.9
3	**5a** + 6 C_2H_6 →  + 5 C_3H_8	-27.9
4	**5'a** + 6 C_2H_6 →  + 5 C_3H_8	-47.6
5	**1b** +  → **1a** + 	-0.9
6	**5b** +  → **5a** + 	-16.3
7	**5'b** +  → **5'a** + 	-14.2

[a] In kcal·mol; $\Delta H_f°$ (MNDO)'s were used in the calculation (see Table I).

Next we will turn to the influence of chlorine substitution. The results of entries 1, 2, and 5 reveal that chlorine substitution does not exert much influence on the SE. Therefore, electronic factors must be responsible for the experimentally observed lower rate of rearrangement of **1b**. A comparison of the two PA's of **1a** and **1b** (Table I) shows that for the latter they are 15.4 kcal·mol^{-1} (PA(**5a**)–PA(**5b**)) and 13.3 kcal·mol^{-1} (PA(**5'a**)–PA(**5'b**)) smaller. As anticipated,[9b] this is a consequence of the destabilization of the cationic intermediate **5**(') by the electron-withdrawing halogen substituents.

Diels–Alder Reactions of [5]Metacyclophanes (1b–e). In general, benzene and its simple derivatives do not engage in Diels–Alder reactions with dienophiles under mild conditions.[20] Obviously, the low reactivity is a consequence of the high activation energy needed to break up the resonance of the aromatic ring. However, this barrier can be lowered by either a decrease of the resonance energy or by an increase in ground-state energy of the aromatic "diene" due to strain or imposed steric factors. In the

(15) Jenneskens, L. W.; De Kanter, F. J. J.; De Wolf, W. H.; Bickelhaupt, F. *Magn. Reson. Chem.* **1986**, *24*, 308.

(16) (a) For the calculation of PA, the experimental $\Delta H_f°$(H^+) = 367.2 kcal·mol^{-1} was used: Olivella, S.; Urpi, F.; Vilarrasa, J. *J. Comput. Chem.* **1984**, *5*, 230. (b) Bowers, M. T. *Gas Phase Ion Chemistry*; Academic Press: New York, 1979; Vol. 2. (c) Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: New York, 1970. (d) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907.

(17) Cf.: Devlin, III, J. I.; Wolf, F.; Taft, R. W.; Hehre, W. J. *Ibid.* **1976**, *98*, 1991.

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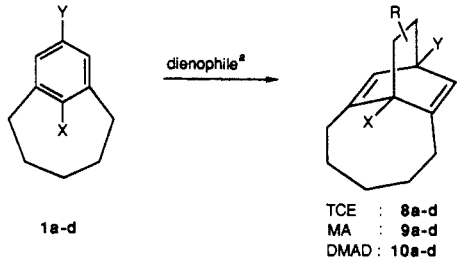
(20) (a) Ciganek, E. *Tetrahedron Lett.* **1967**, 3321. (b) Krespan, C. G.; McKusick, B. C.; Cairns, T. L. *J. Am. Chem. Soc.* **1961**, *83*, 3428. (c) Bryce Smith, D.; Gilbert, A.; McColl, I. S.; Yianni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 951. (d) Arriau, J.; Fernandez, J.; Yianni, P. *J. Chem. Soc., Perkin Trans. 2* **1986**, 2013. (e) Bryce Smith, D.; Gilbert, A.; McColl, I. S.; Drew, M. G. B.; Yianni, P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1147. (f) Cookson, T. L.; Dance, J. *Tetrahedron Lett.* **1962**, 879.

Scheme IV[a]



[a] TCE, tetracyanoethene; MA, maleic anhydride; DMAD, dimethyl acetylenedicarboxylate.

Table III. Conditions and Yields of Diels–Alder Reactions of 1a–e[a]

cyclophane[b]	dienophile: tetracyanoethene	maleic anhydride	dimethyl acetylenedicarboxylate
1a[c]	**8a** 100% 25 °C, <15 min	**9a**, 100% 25 °C, <15 min	**10a**, 100% 25 °C, 5 h
1b	**8b**,[d] 95% 25 °C, 25 h	**9b**,[c] 65% 25 °C, 43 h	**10b**,[d,e] 93% 60 °C, 110 h
1c	**8c**,[d] 59% 25 °C, 25 h	9c,[e] 76% 25 °C, 24 h	**10c**,[d,e] 34% 60 °C, 26 h
1d	**8d**,[d] 95% 25 °C, 25 h	**9d**[f]	**10d**[f]

[a] Cf. Scheme IV. [b] Solvent $CDCl_3$, unless stated otherwise. [c] Reference 9. [d] Solvent C_6D_6. [e] Characterized only by ^1H NMR. [f] Not investigated.

case of the [*n*]metacyclophanes, MNDO calculations[12a] have indicated that the latter does indeed occur: a substantial increase in ground-state energy with decreasing *n* is predicted. Consequently, one anticipates an increase in reactivity with decreasing *n*.

[7]Metacyclophane has been reported to yield a Diels–Alder adduct with hexafluoro-2-butyne at 150 °C.[8] [5]Metacyclophane (**1a**) reacts with a variety of dienophiles under very mild conditions (room temperature).[9a] We observed the formation of Diels–Alder adducts for the 8,11-dihalo[5]metacyclophanes (**1b–d**) with the dienophiles tetracyanoethene, maleic anhydride, and dimethyl acetylenedicarboxylate (Scheme IV).

However, in comparison with the parent compound **1a**, the rate of formation is markedly lower (Table III). Note that only 2,5-adducts were obtained; 1,4-adducts could not be detected. The decrease in reactivity of **1b–d** compared to **1a** can be rationalized to be a consequence of both electronic and steric factors. The presence of the electron-withdrawing halogen substituents will lower the HOMO energy, This is supported by MNDO calculations on **1a** and **1b** (HOMO: **1a**, −8.93 eV; **1b**, −9.28 eV). Furthermore, the increase in size of substituents at C(8) and C(11) in the series **1a–e** will have a retarding influence on the approach of the dienophile. This is evident from the behavior of **1e** which does not react with tetracyanoethene,[14] even at elevated temperature (60 °C, vide infra).

However, other less obvious factors also appear to determine the Diels–Alder reactivity of [*n*]metacyclophanes. For example, [6]metacyclophane[5] and its 9,12-dihalo derivatives[21] do not undergo Diels–Alder reactions, despite the fact that their strain energy is intermediate between that of the corresponding [7]- and [5]metacyclophanes.[12a] In [6]metacyclophanes and their Diels–Alder adducts, the strain has not only the "anti-Bredt" component common to all small cyclophanes, but in addition medium-sized ring strain due to their nine-membered rings, which may influence adduct formation unfavorably.

Photochemical Behavior of [5]Metacyclophanes. Irradiation of **1a–e** in ethanol solution with a Pyrex-filtered low-pressure mercury lamp at room temperature gave a clean and nearly quantitative rearrangement to **3a–e**, respectively (Scheme V). In the case of **1b–d**, trace amounts of another type of product were

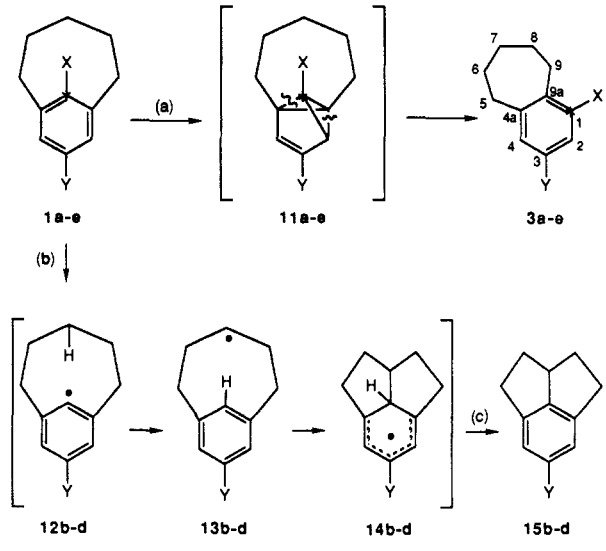
(21) Jenneskens, L. W. Ph.D. Thesis, Vrije Universiteit, Amsterdam, The Netherlands, 1986.

Table IV. ^1H NMR Data of **18**

	δ (ppm)		
H(11), H(41)	3.23		
H(12), H(42)	2.84		
H(21), H(31)	1.60		
H(22), H(32)	2.36		
H(2a)	3.33		
	J(HH)[a] (Hz)	Θ[b] (deg)	J(HH)[c] (Hz)
H(11), H(12)	−15.5		
H(11), H(21)	11.5	21.7	8.4
H(11), H(22)	6.1	139.6	6.7
H(11), H(2a)	1.5		
H(11), H(41)	0.5		
H(12), H(21)	7.8	21.2	8.7
H(12), H(22)	0	−96.7	0.2
H(21), H(22)	−11.9		
H(21), H(2a)	9.8	24.9	8.2
H(22), H(2a)	6.5	144.1	7.9

[a] Experimental value (spectrum simulation). [b] Dihedral angles (Θ) taken from MNDO structure. [c] Calculated according to $^3J(HH) = A\cos^2\Theta - 0.28$ (A = 10 and A = 12 for Θ = 0–90° and 90–180°, respectively; Hesse, M.; Meier, H.; Zech, B. *Spektroskopische Methoden in der Organischen Chemie*; Thieme Verlag, 1979).

Scheme V[a,b]



[a] (a) *hν*, (b) *hν*, −X·, (c) −H·. [b] * = ^{13}C label in **1b** and **3b**.

detected; on the basis of their spectral data, their structure was assigned as that of 6-halo-2,2a,3,4-tetrahydro-1*H*-cyclopent[*c*,*d*]indene (**15**, Scheme V).

The photolytic transformation of **1a–e** to **3a–e** could occur via two plausible pathways. The first and trivial one would be the acid-catalyzed rearrangement (vide supra). However, **1a–e** are stable in ethanol solution at room temperature without irradiation. Even more compelling is the observation that on irradiation, **1e** rearranges to **3e** with retention of the *tert*-butyl group, whereas acid catalysis leads to its complete loss (vide supra). Furthermore, in contrast to their behavior on acid treatment, **1b–d** gave no **4b–d**. Therefore, we strongly prefer a second mechanism, which proceeds via a benzvalene intermediate **11**. Under the reaction conditions, the latter apparently isomerizes to **3**. Unambiguous corroboration in favor of the benzvalene mechanism came from the irradiation of labeled [11-^{13}C]**1b**. It leads to [1-^{13}C]**3b** in which the connectivity between the labeled carbon (δ = 133.8 ppm, see Experimental Section) and its substituent is unchanged (Scheme V); in contrast, the acid-catalyzed transformation of the same [11-^{13}C]**1b** gave the isotopomer [9a-^{13}C]**3b**, in which the label is separated from chlorine and attached to the pentamethylene chain (Scheme II). Attempts to characterize the benzvalene intermediate **11** spectroscopically at low temperature (−60 °C) were so far unsuccessful. Presumably, benzvalene formation is facilitated by the distorted geometry of the benzene ring; as it were, the

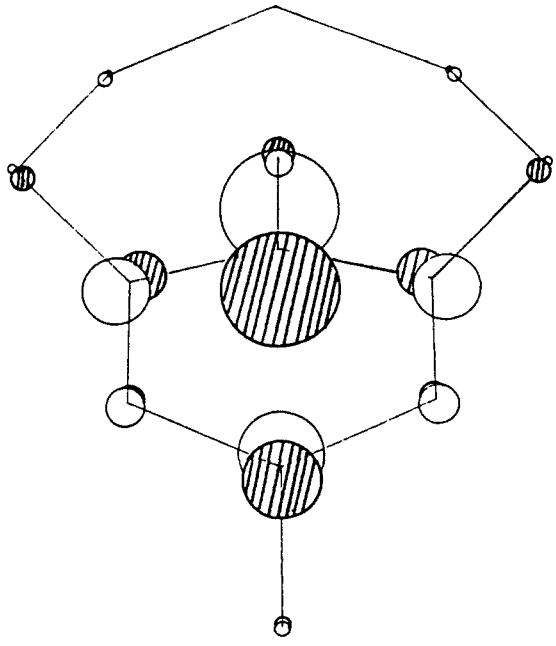


Figure 1. Plot of the LUMO of 8,11-dichloro[5]metacyclophane (**1b**).

strained bridge "pulls" the bridgehead carbons together. It is noteworthy that higher homologues of **1** do not undergo an analogous photolytic rearrangement. However, [6]metacyclophene[22] has been reported to isomerize in the same fashion, undoubtedly because the double bond in the bridge increases the strain sufficiently.

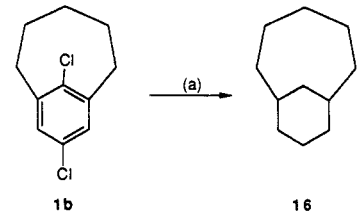
The formation of the minor products **15** from **1b–d** can be rationalized by invoking a competitive radical pathway, i.e., photolytic scission of the carbon–halogen bond[23] C(11)–X which leads to the radical intermediate **12**. Abstraction of the more weakly bonded hydrogen from the central methylene group of the bridge gives **13**. MNDO/HE (half electron) calculations[24] on the intermediate radical **12b** indicate that the distance between C(11), on which the aryl-σ radical is located, and the inner hydrogen atom of the central methylene group of the bridge is very short (d[C(11)···H] = 2.85 Å; sum of van der Waals radii d[C···H] = 3.30 Å). Intermediate **13** undergoes an intramolecular attack of the alkyl radical on the aromatic ring to furnish **14**. Loss of hydrogen from the latter yields **15** (Scheme V). Analogous transannular coupling products were formed exclusively on irradiation of higher homologues of **1**, which contain a halogen substituent between the bridgehead carbon atoms;[5] in this case, strain is apparently insufficient to make benzvalene formation competitive.

A comparison of the calculated MNDO geometry of **12b** with that of **1b**[12a] shows only minor changes on homolytic scission of the C(11)–X bond. The LUMO of **1b**, which is involved in the photochemical reaction, possesses stronger antibonding character in the C(11)–X bond than in the C(8)–Y bond, thus facilitating scission of the former (Figure 1).

For the unstrained analogue 2,5-dichloro-*m*-xylene, MNDO predicts for both the C–X and C–Y bond essentially the same degree of antibonding character in the LUMO.

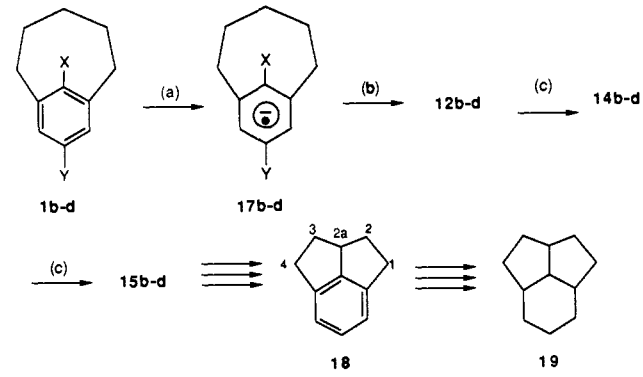
Catalytic Hydrogenation of 1b. Since halobenzenes are conveniently dehalogenated by catalytic hydrogenation under mild conditions,[25] we attempted the dehalogenation of 8,11-dichloro-[5]metacyclophane (**1b**) with the objective to open a new and better route to the parent hydrocarbon **1a**. However, a rapid uptake of 5 molar equiv of hydrogen was observed when an ethanolic solution of **1b** containing a catalytic amount of 5% Pd/C was subjected to hydrogenation under atmospheric pressure at room temperature. After workup, only one product was isolated and identified as bicyclo[5.3.1]undecane (**16**, Scheme VI).[26] Obviously, **1b** is almost instantaneously dehalogenated and hydrogenated; the strain is too high to accomplish the partial reduction of **1b** to **1a**. We have not investigated the sequence in which dehalogenation and hydrogenation occur.

Scheme VI[a]



[a] (a) 5% Pd/C, H_2, C_2H_5OH.

Scheme VII[a]



[a] (a) NaH/Ni(OAc)$_2$; SET; (b) $-X^-$; (c) cf. Scheme V.

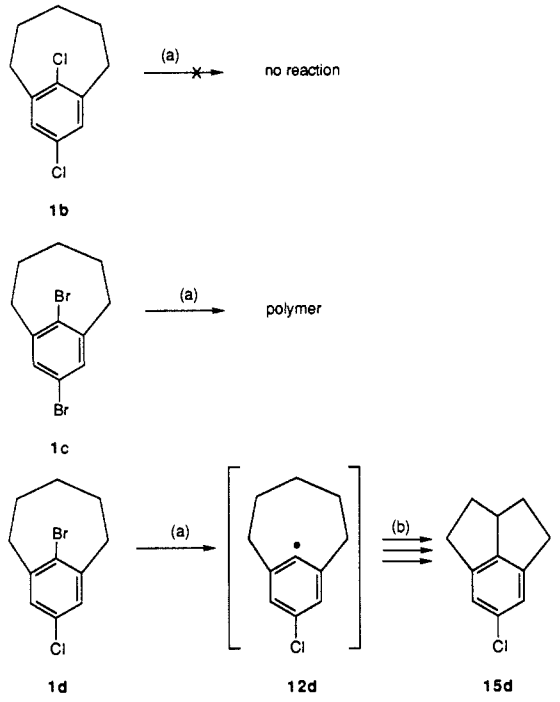
Reactivity of 1b–d toward NaH/Ni(OAc)$_2$. The dehalogenation of halogen-substituted benzene derivatives[27] with complex reducing agents is well established. Therefore this approach seemed to be promising for the desired conversion of **1b–d** to the parent compound **1a**. We have investigated the behavior of **1b–d** toward the complex reducing agent system NaH/Ni(OAc)$_2$/*tert*-amyl alcohol. However, instead of **1a**, another product was isolated in ca. 80% yield and identified as 2,2a,3,4-tetrahydro-1*H*-cyclopent[*c*,*d*]indene (**18**).[28,31] The exclusive formation of **18** from **1b–d** can be rationalized by the mechanism presented in Scheme VII.

Complex reducing agents are known to react via a single-electron-transfer (SET) mechanism.[27] In the case of **1b–d**, SET yields the radical anion **17** which after extrusion of X^- gives the radical **12**. The latter subsequently furnishes **15b–d** in three steps (cf. Scheme V). The second halogen substituent Y is replaced subsequently via the usual pathway.[27] This follows from separate experiments in which **1b** was reacted with deficient amounts of the complex reducing agent. Besides some starting material **1b**, **15b** was isolated; thus the halogen substituent at C(11) is reduced first. The previously mentioned higher antibonding character of the LUMO at the C(11)–X bond is presumably responsible (cf. Figure 1).

With a large excess of reducing agent, instead of **18**, the fully saturated analogue tricyclo[5.3.1.0.^{4,11}]undecane (**19**)[29] was ob-

(22) (a) Goodman, J. L.; Berson, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 5409. (b) Goodman, J. L.; Berson, J. A. *Ibid.* **1985**, *107*, 5424.
(23) (a) Pinhey, J. T.; Rigby, R. D. G. *Tetrahedron Lett.* **1969**, 1267. (b) Eichin, K. H.; Beckhaus, H. D.; Rüchardt, C. *Ibid.* **1980**, *21*, 269.
(24) (a) Clark, T. *Handbook of Computational Chemistry*; Wiley: New York, 1985; Chapter 4. (b) Cf., also: Higgins, D.; Thomson, C.; Thiel, W. *J. Comput. Chem.* **1988**, *9*, 702.
(25) (a) Seltzer, S. *Adv. Alicycl. Chem.* **1986**, *2*, 1. (b) Sauer, J. *Angew. Chem.* **1966**, *78*, 233. (c) Grice, P.; Reese, C. B. *Tetrahedron Lett.* **1979**, *27*, 2563.
(26) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190.
(27) (a) Caubère, P. *Angew. Chem.* **1983**, *95*, 597 and references cited. (b) Guillaumet, G.; Mordenti, L.; Caubere, P. *J. Organomet. Chem.* **1975**, *92*, 43.
(28) (a) Rapoport, H.; Pasky, J. Z. *J. Am. Chem. Soc.* **1956**, *78*, 3788. (b) Lindner, H. J.; Eilbracht, P. *Chem. Ber.* **1973**, *106*, 2268. (c) Eilbracht, P.; Hafner, K. *Angew. Chem.* **1971**, *83*, 802.
(29) Wingard, R. E., Jr.; Russel, R. K.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 7474.

Scheme VIII[a]



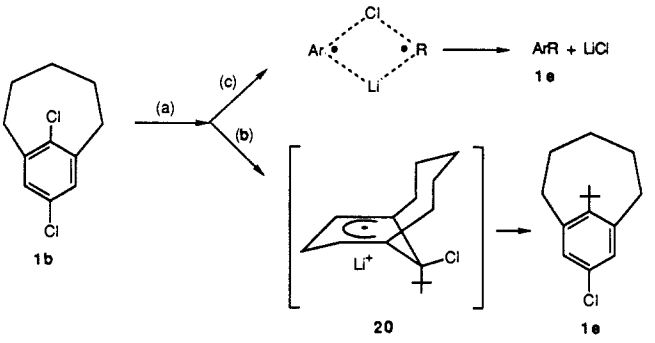
[a] (a) 2*n*-BuLi, CH_3OH; (b) cf. Scheme V.

tained as the only product. Apparently, the considerable strain still present in **18** is large enough to induce further reduction. Note that **18** has been reported to be susceptible to reduction under mild catalytic hydrogenation conditions.[28] It is also known that aromatic compounds can be hydrogenated in the presence of $Ni(OAc)_2$, although with unstrained compounds severe reaction conditions are needed.[30]

Reactivity of 1b–d toward *n*-Butyllithium. In connection with our interest in opening an easy access to [5]metacyclophane (**1a**) from its 8,11-dihalo derivatives, we also investigated their behavior toward *n*-butyllithium. Lithiation, followed by quenching with a proton donor, has been successfully applied for the synthesis of [*n*]metacyclophanes with $n \geq 6$ from their monohalo derivatives.[5] In the case of **1b**, no reaction was observed on treatment with 2 equiv of *n*-butyllithium in *n*-hexane at either room or reflux temperature: only starting material was recovered in ca. 90% yield (Scheme VIII). Note that low reactivity of aryl chlorides toward organolithium reagents is in fact the normal behavior.[32] Under similar conditions, **1c** gave intractable material only; no low molecular weight products could be detected in the reaction mixture (GC/MS). In contrast, **1d** gave as the only product **15d** in ca. 70% yield (Scheme VIII).

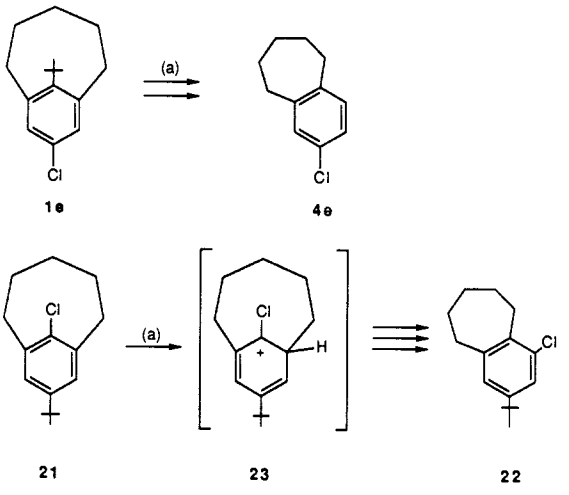
Thus, a surprising influence of the substitution pattern on the course of the reaction is encountered. The formation of intractable (polymeric) material from **1c** and the transannular coupling product from **1d**, respectively, suggests the intermediacy of radicals.[33] In this context, the results of Hirano et al. are of interest: they treated higher homologues of **1**[5] containing a bromine substituent between the bridgehead carbon atoms with *n*-butyllithium, followed by hydrolysis. The [10]metacyclophane derivative afforded the parent hydrocarbon. From [7]–[6]metacyclophane, increasing amounts of transannular coupling product were isolated, besides the desired cyclophane hydrocarbons. Apparently, halogen–lithium exchange leads increasingly to the formation of radical intermediates for halo[*n*]metacyclophanes with decreasing

Scheme IX[a]



[a] (a) 2*t*-BuLi, −70 °C; (b) addition elimination; (c) radical cage formation.

Scheme X[a]



[a] (a) H^+; cf. Scheme II.

n. It would be of general interest to elucidate whether the postulated radicals **12** are direct intermediates in the halogen–metal exchange process or, as in the case of complex hydride reductions (Scheme VII), the result of prior SET.

Reactivity of 1b–d toward *tert*-Butyllithium. After the unsuccessful attempts to convert **1b–d** to **1a** via treatment with *n*-butyllithium, we investigated their behavior toward *tert*-butyllithium. A solution of **1b** in tetrahydrofuran at −70 °C was treated with 2 equiv of *tert*-butyllithium in *n*-hexane. After stirring for 5 h at −70 °C, methanol-*O*-*d* was added. After workup no indication of the desired [$^2H_2$]**1a** could be detected. Instead, 11-*tert*-butyl-8-chloro[5]metacyclophane (**1e**) was isolated in ca. 70% yield (Scheme IX).[14]

Both the exact mass and the ^{1}H-NMR spectrum proved the substitution of one chlorine by the *tert*-butyl group. Formally, two regioisomers, **1e** and **21** are in agreement with these spectroscopic data. A distinction in favor of **1e** was made by its rapid and clean rearrangement at room temperature to **4b** under catalytic influence of trifluoroacetic acid (vide supra). The other regioisomer **21** would furnish **22** as the main product in analogy to the pattern observed for **1b** (Scheme II), because in the protonated intermediate **23**, the *tert*-butyl group is not activated for elimination (Scheme X).

The structural assignment of **1e** was further corroborated by its ^{13}C-NMR spectrum.[15] Most diagnostic is the low field shift of C(11) in comparison with the value calculated by additivity rules ($\Delta\delta$ = 15.4 ppm). Similar deviations from additivity rules were also observed for **1a–d**. The formation of **1e** from **1b** was unprecedented, and its mechanism is not fully elucidated at the moment. However, the following remarkable features of this reaction should be pointed out. Formally, the reaction is a nucleophilic substitution of the chlorine at C(11) by a *tert*-butyl group. At first sight, it is unexpected that this reaction takes place at the highly hindered position C(11), especially as the rather bulky

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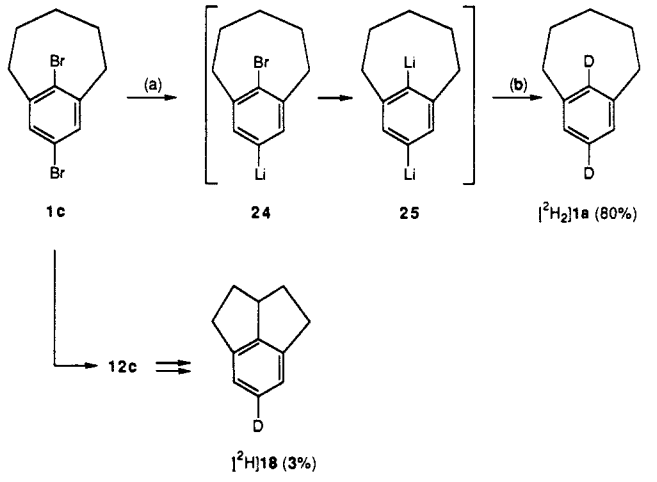
(31) (a) Gruber, R.; Cagniant, D.; Cagniant, P. *Bull. Soc. Chim. Fr.* **1976**, 1599. (b) Gobert, F.; Gruber, R.; Cagniant, D.; Cagniant, P. *Org. Magn. Reson.* **1978**, *11*, 635.
(32) (a) Jones, R. G.; Gilman, H. *Org. React.* **1951**, *6*, 339. (b) Gilman, H.; Brannen, C. G.; Ingham, R. K. *J. Org. Chem.* **1957**, *22*, 685.
(33) Beletskaya, I. P.; Artamkina, G. A.; Reutov, O. A. *Russian Chem. Rev.* **1976**, *45*, 330.

Scheme XI[a]

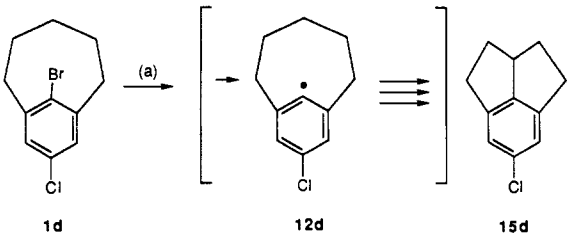


[a] (a) 2*t*-BuLi, −70 °C; (b) CH_3OD.

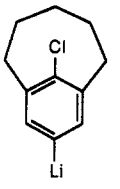
tert-butyl group is introduced between the bridge. As mentioned above, low reactivity of aryl chlorides toward organolithium compounds is the normal behavior.[32] This is illustrated by the retainment of Cl(8) in the presence of excess *tert*-butyllithium. Therefore, the unexpected reactivity must be a consequence of the exceptional structural situation at C(11): the out-of-plane bending of C(11) (α = 26.8°), the opposite tilt (=+13.8°) of Cl(11) toward the oligomethylene bridge, and the slight pyrimidalization at C(11) (sum of bond angles at C(11): X-ray 358.1°).[11,12a] A $S_{RN}1$[34] mechanism can be excluded. It would imply the intermediacy of the aryl radical **12**, which has been found to attack the oligomethylene bridge quite effectively (cf. Scheme V), but such transannular coupling was not detected here (GC/MS). On the other hand, it is conceivable that transannular hydrogen abstraction of the type **12** → **13** (Scheme V) may be avoided by the rapid collapse of a radical cage intermediate (cf. Scheme IX) as proposed in certain lithium–halogen exchange reactions;[35] it can therefore not be fully excluded. However, we consider a reaction by addition–elimination S_N2Ar with **20** as an intermediate to be the most attractive alternative. Normally, such reactions do not occur with unactivated benzene derivatives, but the high strain and the special bonding situation of **1b** may facilitate the process. As indicated before, the LUMO of **1b** (which is involved in the nucleophilic additions step) has orbital coefficients which are larger at C(11) than at C(8), thus indicating higher reactivity toward the nucleophile for the former position. Recently, other examples of addition–elimination reactions involving alkoxide nucleophiles have been found for **1b**, which may be considered as bona fide precedents for the formation of **1e**; the mechanism is discussed in that paper in more detail.[36] Nevertheless, a *tert*-butyl anion remains an exotic candidate for acting as a nucleophile in this type of reaction.

In the case of **1c**, the expected reaction, halogen–lithium exchange, occurred. Treatment with ~2 equiv of *tert*-butyllithium leads to the formation of the intermediate 8,11-dilithio[5]metacyclophane **25** which on quenching with methanol-*O-d* gave [$^2H_2$]**1a** (80% yield).[37] The formation of the side product [^2H]**18** (3%) can be explained by invoking, to a minor extent, the intermediacy of radical **12c**. We assume that in the first step, halogen–lithium exchange occurs at the less hindered position C(8) furnishing **24** which, by the negative charge at the lithium-bearing C(8), is protected against processes such as nucleophilic attack or SET; this is supported by a comparison of the energy of the LUMO of **26** (0.38 eV) with that of **1b** (−0.99 eV).

Scheme XII[a]



[a] (a) 2*t*-BuLi, −70 °C.



26

Unfortunately, this new and convenient synthesis of **1a** is less attractive from a preparative point of view because **2b**, the precursor of **1c**, is only accessible in about 14% yield as a side product in the reaction of dibromocarbene with 1,2-dimethylenecycloheptane.[10]

Compound **1d** followed a different course of reaction under similar conditions. The transannular coupling product **15d** was isolated as the only low molecular weight product in ca. 30% yield (Scheme XII). The expected product, 8-chloro-11-deutero[5]metacyclophane, could not be detected in the reaction mixture. Thus in the absence of a protective negative charge (cf. Scheme XI), SET followed by the formation of the radical **12d** appears to be favored also under these reaction conditions.

Conclusions

The investigation of the chemical behavior of the substituted [5]metacyclophanes revealed a rather unusual reactivity pattern. Compared to normal, planar aromatic analogues, the cyclophanes showed two remarkable trends: (1) for typical aromatic reactions (acid-catalyzed or photochemical rearrangement, reductions, Diels–Alder reactions), a strong rate enhancement was observed; (2) toward organolithium reagents, abnormal reaction pathways are followed, such as nucleophilic substitution, SET, and other radical processes. In view of the overwhelming evidence in favor of essentially undiminished aromatic delocalization,[11,37] this unusual behavior must be ascribed to the special geometry of these small cyclophanes and, in particular, to the dramatic decrease of strain occurring in the initial steps of all of these reactions.

Experimental Section

Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Bruker WH 90 or WM 250 spectrometer as indicated. Carbon magnetic resonance spectra (^{13}C-NMR) were recorded on a Bruker WM 250 spectrometer operating at 62.89 MHz. Products were analyzed by GCMS on a Finnigan 4000 mass spectrometer. Exact mass measurements were performed with a Varian CH5-DF mass spectrometer at an ionization potential of 70 eV. Gas chromatography on an Intersmat P120 with thermal conductivity detector and hydrogen as carrier gas. All boiling and melting points are uncorrected.

Acid-Catalyzed Rearrangement of 1a–e. To a solution of **1** (0.05 mmol) in chloroform-*d* (400 μL), 1 μL trifluoroacetic acid-*d* was added. The rearrangement was followed by ^{1}H NMR spectroscopy. Afterwards the solvent was evaporated under reduced pressure, and the residue was purified by preparative GLC (5% Carbowax on Chromosorb W; 1.5 m). The ratio of **3**:**4** was ca. 2:1 in the case of **1b–d**. The rearrangement was quantitative. **1,3-Dichloro-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (3b)**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21 (d, ^4J(HH) = 2.2 Hz, 1 H),

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7.01 (d, ^4J(HH) = 2.2 Hz, 1 H), 2.99 (m, 2 H), 2.79 (m, 2 H), 1.83 (m, 2 H), 1.63 (m, 4 H); MS m/z (rel intensity) 214 (55, **3b**$^{\bullet+}$) with isotope pattern, 181 (33), 179 (100, [**3b** − Cl]$^+$); calcd for $C_{11}H_{12}{}^{35}Cl_2$ 214.0316, found 214.0314. **1,3-Dibromo-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (3c)**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 (d, ^4J(HH) = 3.2 Hz, 1 H), 7.19 (d, ^4J(HH) = 3.2 Hz, 1 H), 3.03 (m, 2 H), 2.82 (m, 2 H), 1.84 (m, 2 H), 1.63 (m, 4 H); MS m/z (rel intensity) 302 (66, **3c**$^{\bullet+}$) with isotope pattern, 225 (31), 223 (32, [**3c** − Br]$^+$), 144 (66); calcd for $C_{11}H_{12}{}^{79}Br_2$ 301.9306, found 301.9316. **1-Bromo-3-chloro-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (3d)**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.39 (d, ^4J(HH) = 2 Hz, 1 H), 7.03 (d, ^4J(HH) = 2 Hz, 1 H), 3.07 (m, 2 H), 2.82 (m, 2 H), 2.82 (m, 2 H), 1.84–1.51 (m, 6 H); MS m/z (rel intensity) 258 (51, **3d**$^+$) with isotope pattern, 225 (32), 223 (34, [**3d** − Cl]$^+$), 181 (17), 179 (50, [**3d** − Br]$^+$), 115 (100); calcd for $C_{11}H_{12}{}^{79}Br^{35}Cl_2$ 257.9811, found 257.9810.

2-Chloro-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (4b = 4d = 4e = M): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.07 (br s, 1 H), 7.03 (m, 2 H), 2.77 (m, 4 H), 1.93–1.53 (m, 6 H); MS m/z (rel intensity) 180 (48, M$^{\bullet+}$) with isotope pattern, 145 (100, [M − Cl]$^+$); calcd for $C_{11}H_{13}{}^{35}Cl$ 180.0706, found 180.0697. **2-Bromo-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (4c)**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (d, ^4J(HH) = 2.1 Hz, 7.20 and 6.96 (AB system, J(AB) = 7.9 Hz, on A part ^4J(HH) = 2.1 Hz, 2 H), 2.75 (m, 4 H), 1.82 (m, 2 H), 1.62 (m, 4 H); MS m/z (rel intensity) 224 (42, **4c**$^{\bullet+}$) with isotope pattern, 145 (100, [**4c** − Br]$^+$), 115 (47); calcd for $C_{11}H_{13}{}^{79}Br$ 224.1417, found 224.1416.

Diels–Alder Reactions of 1b–d. The Diels–Alder reactions were performed in a NMR tube, containing a solution of **1** (0.1 mmol) in either chloroform-*d* or benzene-*d* (400 μL) and 1 molar equiv of the dienophile tetracyanoethene (TCE), maleic anhydride (MA), or dimethyl acetylenedicarboxylate (DMAD), respectively. In the case of TCE and MA, the reaction was performed at room temperature, with DMAD at 60 °C. The formation of the 2,5-addition products was followed by ^{1}H-NMR spectroscopy (see Table III). The products were characterized by their spectral properties.

Reaction of 1b–d with Tetracyanoethene. 1,10-Dichloro-11,11,12,12-tetracyanotricyclo[7.3.1.0^{3,10}]trideca-2,9(13)-diene (8b): ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.68 (s, 2 H), 2.60–2.20 (m, 4 H), 2.10–1.50 (m, 6 H); calcd for $C_{17}H_{12}{}^{35}Cl_2N_4$ 342.0439, found 342.0433. Anal. Calcd for $C_{17}H_{12}{}^{35}Cl_2N_4$: C, 59.49; H, 3.52. Found C, 59.35; H, 3.54. **1,10-Dibromo-11,11,12,12-tetracyanotricyclo[7.3.1.0^{3,10}]trideca-2,9(13)-diene (8c)**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.27 (s, 2 H), 2.27 (m, 4 H), 1.64 (m, 6 H); calcd for $C_{17}H_{12}{}^{79}Br_2N_4$ 431.9300, found 431.9380. **10-Bromo-1-chloro-11,11,12,12-tetracyanotricyclo[7.3.0^{3,10}]trideca-2,9-(13)-diene (8d)**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.32 (s, 2 H), 2.88–2.33 (m, 4 H), 2.00–1.11 (m, 6 H); MS m/z (rel intensity) 386 (7, **8d**$^{\bullet+}$) with isotope pattern, 258 (24), 223 (10), 179 (100); calcd for $C_{17}H_{12}{}^{79}Br^{35}ClN_4$ 385.9945, found 385.9929.

Reaction of 1b–c with Maleic Anhydride. 12-Oxa-11,13-dioxo-9,15-dichlorotetracyclo[7.6.1.0^{8,9}.0^{10,14}]hexadeca-1(15),8-diene (9b): ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.21 (s, 1 H), 6.06 (s, 1 H), 3.69 (s, 2 H), 3.10–0.80 (m, 10 H); calcd for $C_{15}H_{14}{}^{35}Cl_2O_3$ 312.0330, found 312.0320. **12-Oxa-11,13-dioxo-9,15-dibromotetracyclo[7.6.1.0^{8,9}0^{10,14}]hexadeca-1-(15),8-diene (9c)**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.35 (br s, 1 H), 6.13 (br s, 1 H), 3.76 (br s, 2 H), 3.27–1.38 (m, 10 H).

Reaction of 1b,c with Dimethyl Acetylenedicarboxylate. *cis*-11,12-Bis(carbomethoxy)-1,10-dichlorotricyclo[7.3.1.0^{3,10}]trideca-2,9(13)-diene (10b): ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.57 (s, 2 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.30–0.70 (m, 10 H). ***cis*-11,12-Bis(carbomethoxy)-1,10-dibromotricyclo[7.3.10^{3,10}]trideca-2,9(13)-diene (10c)**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.48 (s, 2 H), 4.27 (s, 3 H), 4.23 (s, 3 H), 3.20–1.50 (m, 10 H).

Irradiation of 1b–e. A solution of **1** (0.5 mmol) in ethanol (10 mL, distilled from Mg/I_2) was irradiated with a medium-pressure mercury lamp (150 W) in a Pyrex vessel for 1 h at room temperature. Afterwards the solvent was evaporated under reduced pressure, and the residue was purified by preparative GLC (5% Carbowax on Chromosorb W, 1.5 m). The rearrangement was nearly quantitative (see text).

6-Chloro-2,2a,3,4-tetrahydro-1*H*-cyclopent[*c*,*d*]indene (15b = 15d). ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.94 (s, 2 H), 3.36 (ttt, ^3J(HH) = 9.8 Hz, ^3J(HH) = 6.5 Hz, ^4J(HH) ca. 1.0 Hz, 1 H), 3.28 (ddddd, ^2J(HH) = −15.5 Hz, ^3J(HH) = 11.5 Hz, ^3J(HH) = 6.1 Hz, ^4J(HH) = 1.5 Hz, ^6J(HH) = 0.5 Hz, 2 H), 2.90 (dd, ^2J(HH) = −15.5 Hz, ^3J(HH) = 7.8 Hz, 2 H), 2.44 (ddd, ^2J(HH) = −11.9 Hz, ^3J(HH) = 6.1 Hz, ^3J(HH) = 6.5 Hz, 2 H), 1.72 (dddd, ^2J(HH) = −11.9 Hz, ^3J(HH) = 11.5 Hz, ^3J(HH) = 7.8 Hz, ^3J(HH) = 9.8 Hz, 2 H); MS m/z (rel intensity) 178 (100, **15b**$^{\bullet+}$) with isotope pattern, 143 (73, [**15b** − Cl]$^+$); calcd for $C_{11}H_{11}{}^{35}Cl$ 178.0549, found 178.0547. **6-Bromo-2,2a,3,4-tetrahydro-1*H*-cyclopent[*c*,*d*]indene (15c)**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.10 (s, 2 H), 3.34 (ttt, ^3J(HH) = 9.8 Hz, ^3J(HH) = 6.5 Hz, ^4J(HH) ca. 1.0 Hz, 1 H), 3.28 (ddddd, ^2J(HH) = −15.5 Hz, ^3J(HH) = 11.5 Hz, ^3J(HH) = 6.1 Hz, ^4J(HH) = 1.5 Hz, ^6J(HH) = 0.5 Hz, 2 H), 2.91 (dd, ^2J(HH) = −15.5 Hz, ^3J(HH) = 7.8 Hz, 2 H), 2.44 (ddd, ^2J(HH) = −11.9 Hz, ^3J(HH) = 6.1 Hz, ^3J(HH) = 6.5 Hz, 2 H), 1.74 (dddd, ^2J(HH) = −11.9 Hz, ^3J(HH) = 11.5 Hz, ^3J(HH) = 7.8 Hz, ^3J(HH) = 9.8 Hz, 2 H); MS m/z (rel intensity) 222 (100, **15c**$^{\bullet+}$) with isotope pattern, 143 (85), [**15c** − Br]$^+$), 128 (82), 115 (29). **1-*tert*-Butyl-3-chloro-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (4e)**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20 (d, ^3J(HH) = 3.2 Hz, 1 H), 7.01 (d, ^3J(HH) = 3.2 Hz, 1 H), 3.05 (m, 2 H), 2.80 (m, 2 H), 1.83 (m, 2 H), 1.62 (m, 4 H), 1.41 (s, 9 H); MS m/z (rel intensity) 236 (39, **4e**$^{\bullet+}$) with isotope pattern, 221 (88, [**4e** − CH_3]$^+$), 181 (34), 179 (100), 144 (18); calcd for $C_{15}H_{21}{}^{35}Cl$ 236.1332, found 236.1338.

Reaction of 1b–d with NaH/Ni(0). The reduction was performed according to the procedure described by Guillaumet et al. in ref 27b. After workup the residue was purified by preparative GLC (5% Carbowax on Chromosorb W; 1.5 m). **2,2a,3,4-Tetrahydro-1*H*-cyclopent[*c*,*d*]indene (18).**[28] The yield was ca. 80%. ^{1}H NMR (250 MHz, $CDCl_3$, coupling constants (J(HH)) were obtained by spectrum simulation with the PANIC program from Bruker, see Table IV); MS m/z (rel intensity) 144 (60, **18**$^{\bullet+}$), 129 (100, [**18** − CH_3]$^+$), 115 (35); calcd for $C_{11}H_{12}$ 144.0939, found 144.0944. **Tricyclo[5.3.1.0.^{4,11}]undecane (19)**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.11–0.53 (m, 18 H); MS m/z (rel intensity) 150 (22, **18**$^{\bullet+}$), 122 (110, [**18** − C_2H_4]$^+$); calcd for $C_{11}H_{18}$ 150.1409, found 150.1401. Compound **19** was identical with the product obtained by catalytic hydrogenation of **18**.[28]

Catalytic Hydrogenation of 1b. A vigorously stirred suspension of **1b** (0.23 mmol) in ethanol (5 mL) and 5% Pd/C (10 mg) was hydrogenated at room temperature and at atmospheric pressure. Within 5–10 min 5 molar equiv of hydrogen were absorbed. After filtration of the reaction mixture, the filtrate was concentrated under reduced pressure. The residue was purified by preparative GLC (15% SE-30 on Chromosorb W, 1.5 m) to yield **16** as a colorless liquid in ca. 95% yield. **Bicyclo-[5.3.1]undecane (16)**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.42–1.00 (m, 20 H); MS m/z (rel intensity) 152 (24, **16**$^{\bullet+}$), 109 (35), 96 (74), 81 (78), 67 (100). The ^{13}C-NMR spectrum of **16** was in agreement with already reported data.[26,29] ^{13}C-NMR (62.89 MHz, $CDCl_3$) δ 32.8, 31.7, 31.6, 31.3, 28.2, 25.5, and 16.0 ppm.

Reaction of 1b–d with *n*-Butyllithium. To a solution of **1** (0.23 mmol) in dry *n*-hexane (10 mL) was added 2 molar equiv of *n*-butyllithium in *n*-hexane under a nitrogen atmosphere. The mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was quenched with D_2O. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. This residue was purified by preparative GLC (5% Carbowax on Chromosorb W, 1.5 m). The reaction was also performed at room temperature for **1c** and **1d** with tetrahydrofuran (10 mL) as solvent. For results, see text and Scheme VIII.

Reaction of 1 with *tert*-Butyllithium. A solution of **1** (0.23 mmol) in dry tetrahydrofuran was cooled to −70 °C (dry ice–acetone) under an argon atmosphere. Under vigorous stirring, 2 molar equiv of *tert*-butyllithium in *n*-hexane was slowly added. On addition, the colorless solution turned bright yellow-orange. Stirring at −70 °C was continued for 5 h. Afterwards, 4 molar equiv of methanol-*O*-*d* was added, and the temperature was slowly raised to room temperature. Diethyl ether (10 mL) was added, and the combined organic layer was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated carefully under reduced pressure. The residue was purified by preparative GLC (5% Carbowax on Chromosorb W, 1.5 m).

11-*tert*-Butyl-8-chloro[5]metacyclophane (1e): ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.56 (s, 2 H), 3.14 (ddd, ^2J(HH) = −12.1 Hz, ^3J(HH) = 12.1 Hz, ^3J(HH) = 3.3 Hz, 2 H), 2.60 (ddd, ^2J(HH) = −12.3 Hz, ^3J(HH) = 3.3 Hz, ^3J(HH) = 3.3 Hz, 2 H), 1.83 (m, 2 H), 1.50 (m, 1 H), 1.38 (s, 9 H), 1.30 (m, 1 H), 0.17 (m, 2 H); ^{13}C-NMR (62.89 MHz, $CDCl_3$) δ 156.8 (s, C(11)), 147.0 (s, C(6,10)), 131.1 (s, C(8)), 121.9 (d, J(CH) = 165 Hz, C(7,9)), 42.8 (t, J(CH) = 129.4 Hz, C(1,5)), 40.8 (t, J(CH) = 129.1 Hz, C(2,4)), 38.2 (s, $-C(CH_3)_3$), 35.6 (q, J(CH) = 129.0 Hz, $-CH_3$), 23.5 (t, J(CH) = 121.8 Hz, C(3)); UV [cyclohexane, λ_{max} in nm (log ϵ) 270 (3.45), 280 (3.40), 320 (3.15); MS m/z (rel intensity) 238 (4), 236 (13, **1e**$^{\bullet+}$), 57 (100); calcd for $C_{15}H_{21}{}^{35}Cl$ 236.1332, found 236.1325.

8,11-Dichloro[11-^{13}C][5]metacyclophane ([11-^{13}C]1b). Compound [11-^{13}C]**1b** was prepared by using $^{13}CHCl_3$ (10% enriched) in the dichlorocarbene addition to 9,9-dichlorobicyclo[5,3,8]dec-1(7)-ene, leading to **2a**, the precursor of **1b**.[38] The labeled **2a** was transformed to labeled **1b** according to the procedure described in ref 10. **9,9,11,11-Tetrachloro[11-^{13}C]tricyclo[5.3.1.0^{1,7}]undecane ([11-^{13}C]2a)**: ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 91.9 (s, C(9)), 79.3 (s, C(11)), 59.4 (t, J(CH) = 138 Hz, C(8,10)), 45.0 (s, C(1,7)), 32.6 (t, J(CH) = 127 Hz, C(4)), 31.2 (t, J(CH) = 130 Hz, C(3,5) or C(2,6)), 26.0 (t, J(CH) = 129 Hz, C(2,6) or C(3,5)). The signal at δ = 79.3 ppm was strongly enchanced, in

agreement with data reported for its benzoannulated analogue.[25c] **8,11-Dichloro[11-^{13}C][5]metacyclophane ([11-^{13}C]1b)**: ^{13}C NMR (62.89 MHz, $CDCl_3$). An enhancement of the signal assigned to C(11) (δ = 141.4 ppm) was observed.[15] Compound [11-^{13}C]**1b** rearranged either by acid or by irradiation into [^{13}C]**3b** as major product. **1,3-Dichloro-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (3b)**: ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 147 (s, C(5a)), 139.3 (s, C(9a)), 133.8 (s, C(1)), 128.8 (s, C(3)), 127.5 (d, J(CH) = 164.2 Hz, C(2)), 126.6 (d, J(CH) = 170.3 Hz, C(4)), 36.6 (t, $-CH_2-$), 32.7 (t, $-CH_2-$), 32.1 (t, $-CH_2-$), 30.2 (t, $-CH_2-$), 27.8 (t, $-CH_2-$), 26.8 (t, $-CH_2-$). The coupling constants of the oligomethylene bridge (J(CH)) could not be assigned unambiguously due to overlap of the signals. The signals of the aromatic part of **3b** were assigned on the basis of coupling patterns, intensity considerations, and additivity rules.[39] The ^{13}C-NMR spectrum of [^{13}C]**3b** was identical with that of **3b** except that, in the case of the acid-catalyzed rearrangement C(9a) (δ 139.3 ppm) and in the case of the irradiation, C(1) (δ 133.8 ppm) was enhanced.

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Appendix. ^{1}H-NMR Spectroscopy of 18

The easy access to **18** from **1b** allowed us to reinvestigate its spectral properties more thoroughly. In Table IV, the ^{1}H-NMR spectrum of **18** and assignments based on spectrum simulations are presented. The ^{1}H-NMR spectrum of the aliphatic protons could only be simulated by invoking additional long-range couplings and by assigning some vicinal coupling constants a value of 0 Hz, implying a dihedral angle between those protons close to 90°. This is supported by a MNDO calculation on **18** (see Supplementary Material); a satisfactory agreement is found between the MNDO structure of **18** and the X-ray crystal structure of its 5-carboxylic acid derivative.[28b] In line with the spectral analysis, both structures have dihedral angles between H(12)/H(22) and H(52)/H(42) close to 90°.

Supplementary Material Available: MNDO structure and a table of bond lengths and valence angles for **18** (1 page). Ordering information is given on any current masthead page.

DNA–Metal Binding by Antitumor-Active Metallocene Dichlorides from Inductively Coupled Plasma Spectroscopy Analysis: Titanocene Dichloride Forms DNA–Cp_2Ti or DNA–CpTi Adducts Depending on pH

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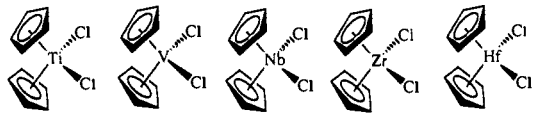
Abstract: Inductively coupled plasma (ICP) spectroscopy is used to measure the DNA–metal binding of the antitumor agents Cp_2TiCl_2, Cp_2VCl_2, Cp_2NbCl_2, and *cis*-$(H_3N)_2PtCl_2$ and of Cp_2ZrCl_2 and Cp_2HfCl_2 in 10 or 110 mM sodium perchlorate with an initial phosphorus to metal ratio of 10:1. All the metals of these complexes bind DNA except vanadium from vanadocene dichloride. There is no release of metal when isolated DNA–metal adduct is dissolved in fresh 10 mM sodium perchlorate for up to 48 h. DNA binding studies using ^{3}H-labeled titanocene dichloride are consistent with a DNA–Cp_2Ti adduct at pH 5.3 and a DNA–CpTi adduct at pH 7.0. A DNA–titanium adduct is also formed from $CpTiCl_3$ and DNA in 10 mM sodium perchlorate with an initial phosphorus to metal ratio of 20:1.

The metallocene dichlorides, Cp_2TiCl_2, Cp_2VCl_2, Cp_2NbCl_2, and Cp_2MoCl_2, exhibit antitumor activity for a wide spectrum of murine and human tumors.[1,2] Similar screening tests reveal



sporadic antitumor activity for $CpTiCl_3$, Cp_2TaCl_2, and Cp_2WCl_2 and no antitumor activity for Cp_2ZrCl_2 and Cp_2HfCl_2.[3] Administration of titanocene dichloride or vanadocene dichloride causes cell gigantism and inhibits DNA synthesis more than protein synthesis; thus, it is reasonable that inhibition of replication is responsible for the antitumor activity of these compounds.[1e] The first hypothesis proposed to explain the antitumor activity of the metallocene dichlorides assumed the cytotoxicity resulted from the metallocene dichlorides binding with DNA via DNA–cisplatin-like adducts.[1e,4,5] This postulate was based on structural similarities noted for the most active metallocene dichloride antitumor agents and cisplatin. The pseudotetrahedral ligand geometries of these metallocene dichlorides and the square-planar geometry of cisplatin are very different, but the complexes have similar Cl–M–Cl bond angles. However, the aqueous chemistry of cisplatin and the metallocene dichlorides differ substantially. The first and second chloride hydrolysis rates for cisplatin are slower than those of Cp_2TiCl_2, Cp_2VCl_2, Cp_2ZrCl_2, and Cp_2MoCl_2.[6] Also, the ammine ligands of cisplatin are essentially inert to hydrolysis,[5] whereas the η^5-cyclopentadienyl ligands of the metallocene dichlorides hydrolyze with rates that depend on the central metal atom and pH. The relative η^5-cyclopentadienyl

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