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Synthesis and anomalous structure–reactivity relationship of 8,11-dichloro[5]metacyclophan-3-one

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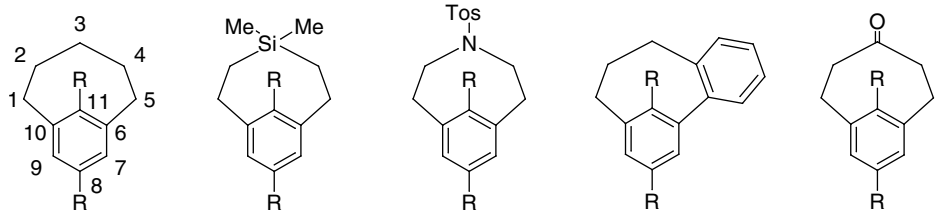
Abstract—The synthesis, structural characterisation, and reactivity of the title compound are reported. It was prepared in order to investigate the effects of incorporation of an sp^2-centre in the bridge of a [5]metacyclophane on its structure and reactivity. An X-ray crystal structure of the cyclophanone demonstrates that the benzene ring is distorted to the same extent as in the hydrocarbon parent compound, while there is less strain in the bridge. Nevertheless, the cyclophanone displays a reduced reactivity in Diels–Alder reactions, which is tentatively ascribed to transition state effects. Calculations indicate that in spite of the close proximity between the ketone functionality and the benzene ring, there are no π–π interactions between them. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Although small [*n*]metacyclophanes ($n \leq 6$) have been known for some time, their chemistry has still not ceased to intrigue many scientists.[1–3] [5]Metacyclophane (**1a**; Fig. 1) is the smallest homologue which can be isolated at room temperature; its pentamethylene bridge causes a boat shape deformation of the benzene ring.[4–6] The severely bent benzene ring is believed to be the origin of the observed high reactivity of [5]metacyclophanes, for instance in Diels–Alder reactions occurring at room temperature and in unusual nucleophilic aromatic substitutions without the aid of activating substituents.[7–9] Despite its high reactivity, **1a** and its halogenated derivatives (like **1b**) are still fully aromatic: they display a normal ring current effect, and there is no evidence for bond alternation in the benzene ring.[4,6,10–13]

As expected, the incorporation of silicon in the bridge as in **2a/b** results in relief of strain due to the longer C–Si bond (1.89 Å)[14] versus C–C bond (1.56 Å).[6] According to the X-ray crystal structure determination of **2b**, the increased length of the bridge allows a decrease in the total bending of the benzene ring (cf. Fig. 2: $\alpha+\gamma=29.9$–$31.0°$) compared to that of **1b** (38.8°), which is accompanied by a marked decrease in reactivity.[14,15] On the other hand, the incorporation of nitrogen in the bridge would be expected to have the opposite effect. Recently, we reported the synthesis and X-ray crystal structure determination of an *N*-tosyl protected 3-aza[5]metacyclophane derivative (**3b**).[13] The



1a/b **2a/b** **3a/b** **4a/b** **5a/b**

Figure 1. (**a**) R=H, (**b**) R=Cl.

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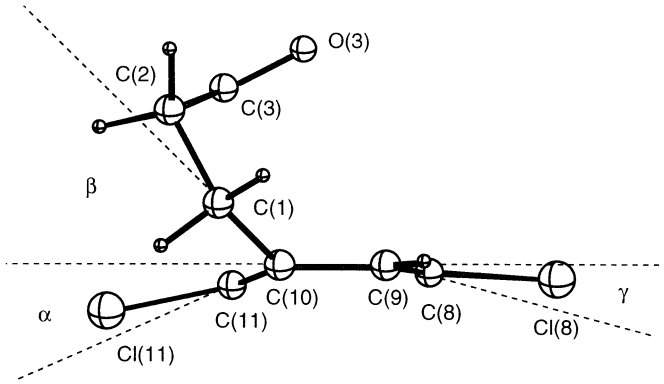


Figure 2. Side view of the crystal structure of **5b**.

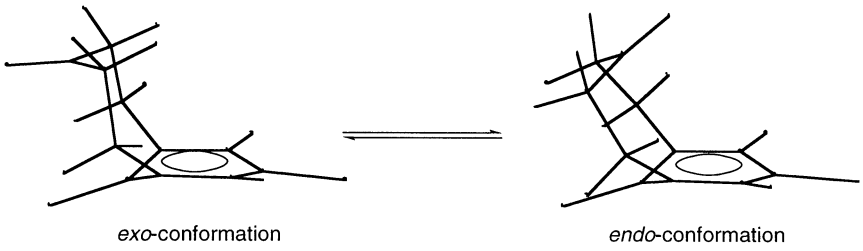


Figure 3. Equilibrium between the *exo*- and the *endo*-conformers of **5b**.

X-ray crystal structure shows that the total bending of the benzene ring in **3b** is indeed larger than in **1b** (39.7°), though less than expected on the basis of the shorter C–N bond length (1.47 Å). Even more surprising was the observation that **3b** was 5–10 times *less reactive* in Diels–Alder reactions than carbon analogue **1b**, despite the *increase* in the deformation of the benzene ring. It was believed that the decrease in reactivity is due to a substantial decrease in strain in the bridge; incorporation of the (nearly planar) tosylamide group results in a reduction of torsional strain and a considerable decrease in angular strain. A second strategy we have pursued in an attempt to increase the strain of a [5]metacyclophane involves the introduction of benzoannelation at the bridge. Indeed, the [5]metacyclophane derivative **4b**, which exists exclusively in the *endo*-conformation (see Fig. 3), displayed the expected increase in reactivity; in Diels–Alder reactions, it was approximately 20 times more reactive than **1b**.[16a] However, the total deformation of the *meta*-substituted benzene ring ($\alpha+\gamma=38.9°$) is nearly identical to that of **1b**.[16b] Furthermore, DFT calculations have shown that the strain energies (SEs) of **1b**-*exo* (SE=182.4 kJ mol^{-1}) and **4b**-*endo* (SE=180.6 kJ mol^{-1}) are practically the same.[17] Therefore, it was concluded that an increase of the strain energy due to a reduction of the length of the bridge is compensated by a reduction of the angular strain. These results showed that our earlier simple hypothesis that the aromatic ring acts a soft spring and therefore absorbs more strain, while the bridge can be considered as a rigid clamp,[18] had to be amended.

In order to further analyse the effects of strain in the bridge on the reactivity of the system as a whole, we synthesised a novel [5]metacyclophane derivative with an sp^2-centre at the central position in the bridge: 8,11-dichloro[5]metacyclophan-3-one (**5b**; Fig. 1); furthermore, **5b** was of interest because of potential interactions between the carbonyl group and the aromatic ring.

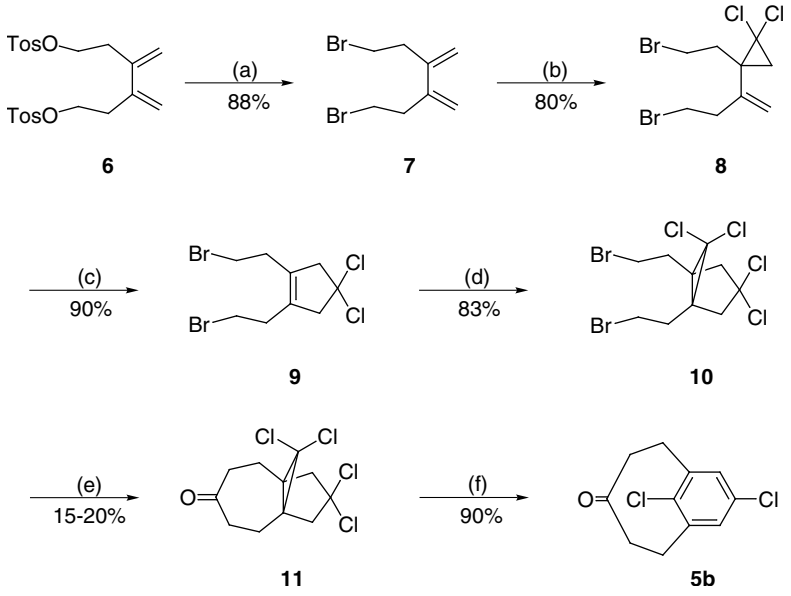
2. Results

2.1. Synthesis

Starting material for the synthesis of **5b** was the ditosylate **6**[13] (Scheme 1). Reaction of **6** with LiBr yielded **7**. Dichlorocarbene addition to **7** by the method of Skattebøl[19] gave **8**, which was converted to **9** by Flash Vacuum Thermolysis (FVT).[20] Dichlorocarbene addition to **9** by the method of Makosza[21,22] gave **10**, which was cyclised with tosylmethylisocyanide (TosMIC)[23–26] to give the propellane **11**. Finally, cyclophanone **5b** was prepared from **11** by double HCl elimination; whereas attempted elimination with *t*-BuOK in DMSO was unsuccessful, the use of $AgClO_4$ and lutidine in THF[5,27] did furnish the desired **5b** in 70–90% yield.

2.2. X-Ray crystal structure determination of 5b

Recrystallisation of **5b** from CH_2Cl_2 gave crystals suitable for X-ray crystal structure determination. Although, in solution, the *exo*-conformation is clearly favoured over the *endo*-conformation (cf. Fig. 3), in the crystalline state only the *endo*-conformer was observed. So far, only one example has been reported of an X-ray crystal structure involving the normally less stable *endo*-conformation: the [5]metacyclophane derivative **4b** (Scheme 1).[16b] Fig. 2 shows a side view of the X-ray crystal structure of the *endo*-conformer of **5b**



Scheme 1. (a) LiBr, acetone, 12 h, Δ; (b) $CHCl_3$, *t*-BuOK, benzene, rt; (c) FVT, 480°C, 5×10^{-5} mbar; (d) $CHCl_3$, PTC, NaOH (50%); (e) NaH, TosMIC, DMSO/Et_2O; (f) $AgClO_4$/lutidine, THF.

with the projected deviation angles α, β, and γ. In Table 1, selected structural data are presented for **1b**-*exo*, **3b**-*exo*, and **5b**-*endo*.

Although **1b** and **5b** appear to be similar at first glance, there are noticeable differences. The C(1)–C(2) bond length as well as the C(1)–C(10) bond length are slightly elongated in **5b**. The C(2)–C(3) bond (1.5466 (19) Å) also appears to be relatively long compared to those reported for other ketones (average 1.509 Å).[28–30] However, the largest differences between **1b** and **5b** are observed in the bridge angles. The angles at C(1) to C(3) in **1b** imply a considerable amount of angular strain for sp^3-hybridised carbon atoms, while in **5b** the angles at C(1) and C(2) are closer to a normal tetrahedral value of 109.5°; the angle at C(3) in **5b** (120.65 (17)°) has a normal value for a carbonyl group.[29] The sum of the angles at C(3) is 359.95°, indicating the absence of pyramidalisation. The CO bond length in **5b** (1.2107 Å) falls in the range reported for cycloalkanone derivatives (1.211 Å for cyclohexanone,[28] 1.193–1.220 Å for cycloheptanones[29,30]). In contrast to the bridges, the benzene rings of **1b** and **5b** are equally deformed; the total bending of the benzene ring ($\alpha+\gamma$; Fig. 2) is 38.8° for **1b** and 38.5° for **5b**. The individual values of α and γ are also similar. Only β, the projected angle between the benzylic substituent and the plane defined by C(6)C(7)C(9)C(10), is smaller in **5b** (46.3°) compared to **1b** (48.0°), indicating a slight relief of strain.

Table 1. Selected bond lengths (Å) and angles (deg) of **1b** (X=CH_2), **3b** (X=N-Tos), and **5b** (X=CO) (esd in last digit in parentheses)

	1b-*exo*	**3b**-*exo*	**5b**-*endo*
C(1)–C(2)	1.569 (3)	1.560 (4)	1.578 (2)
C(2)–X(3)	1.566 (3)	1.486 (4)	1.5466 (19)
C(1)–C(10)	1.506 (3)	1.504 (4)	1.516 (2)
C(6)–C(7)	1.400 (3)	1.385 (4)	1.3957 (19)
C(7)–C(8)	1.389 (3)	1.371 (5)	1.3883 (18)
C(10)–C(11)	1.391 (2)	1.399 (4)	1.3900 (16)
C(10)–C(1)–C(2)	104.7 (2)	103.7 (2)	107.28 (12)
C(1)–C(2)–X(3)	121.9 (3)	114.9 (2)	115.73 (13)
C(2)–X(3)–C(4)	122.2 (2)	121.9 (2)	120.65 (17)
α	26.8	27.4	26.6
β	48.0	48.7	46.3
γ	12.0	12.3	11.9

2.3. Spectroscopic properties of 5b

The ^{1}H NMR spectrum of **5b** shows the characteristic chemical shift of the aromatic protons of a dichloro[5]metacyclophane derivative at 6.9 ppm.[10] From a Karplus analysis of the ^{1}H NMR signals of the bridge at room temperature in $CDCl_3$, it was deduced that **5b** exists as an equilibrium mixture of the two possible bridge conformers: *exo* and *endo* (Figs. 3 and 4).

Variable temperature NMR measurements and line shape analysis of the ^{1}H NMR spectra revealed that, at 206 K, the conformational ratio *exo*/*endo* is 80:20, while in the case of **1b** this ratio is 88:12.[31] The thermodynamic parameters for the conformational exchange of **5b** are: $\Delta H^{\ddagger}$=58.2 kJ mol^{-1}, $\Delta S^{\ddagger}$=15.9 J mol^{-1} K^{-1} (**1b**:[31] $\Delta H^{\ddagger}$= 48.5 kJ mol^{-1}, $\Delta S^{\ddagger}$=−23.0 J mol^{-1} K^{-1}). The conformational equilibrium of **5b** appeared to be slightly temperature dependent. Whereas our earlier observations on **1b** suggested that its equilibrium was temperature independent,[31] a closer re-examination of the ^{1}H and ^{13}C NMR spectra of **1b** revealed that this compound displayed a

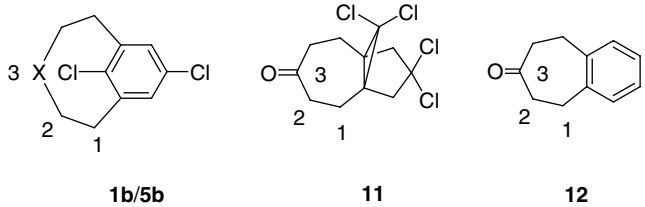


Figure 4. Atom numbering used for **1b**, **5b**, **11** and **12** in Table 2.

Table 2. ^{13}C NMR shifts (δ [ppm]; $CDCl_3$) and CO stretching frequencies (ν [cm^{-1}]; KBr) of cyclophanes **1** and **5b** and reference compounds **11** and **12**

	δ C(1)	δ C(2)	δ C(3)	ν (C=O)
5b-*endo*	33.8	43.2	210.6	1674
5b-*exo*	36.0	52.6	214.1	1674
1b-*endo*[6,14]	34.9	34.5	21.2	–
1b-*exo*[6,14]	40.5	41.6	25.2	–
11	24.6	41.2	210.4	1698
12	30.4	44.4	211.2	1699

similar temperature dependence as **5b**. The differences between the free enthalpies of the *exo*- and *endo*-conformations of **1b** and **5b** are, however, small: **1b**, $\Delta H^0 = -3.05$ kJ mol^{-1}, $\Delta S^0 = 2.1$ J mol^{-1} K^{-1}; **5b**, $\Delta H^0 = -3.14$ kJ mol^{-1}, $\Delta S^0 = -1.8$ J mol^{-1} K^{-1}. The conformational equilibrium of **5b** depends not only on the temperature, but also on the solvent. While in $CDCl_3$ at 206 K the *exo*/*endo* ratio is 80:20, in THF-d_8 and acetone-d_6 these ratios are 88:12 and 84:16, respectively, showing a slight preference for the *exo*-conformation in more polar solvents.

From the ^{13}C NMR data (Table 2) it follows that the differences between the *exo*- and *endo*-conformations of **5b** are comparable with those found for **1b**. In the *endo*-conformation, C(1) to C(3) are shielded compared to the *exo*-conformation. This effect is most pronounced in the case of C(2), where $\Delta\delta$ is as large as 9.4 ppm in **5b**. The shielding effect at C(2) in **5b** is also apparent if one compares the chemical shifts in the two conformers (δ 43.2 and δ 52.6) with those reported for several cycloalkanones: δ 42.0 for cyclohexanone to δ 44.0 for cyclooctanone.[32] Whereas C(2) in **5b**-*endo* is similarly shielded as in **11**, in **5b**-*exo* it is clearly deshielded; the same trend is observed for **1b**. The chemical shift of the carbonyl group in **5b**-*exo* (δ 214.1) fits nicely with those reported for several cycloalkanones.[32] Thus, apart from obvious differences, incorporation of a carbonyl group in the bridge of a [5]metacyclophane has no unusual effects on the ^1H and ^{13}C NMR spectra.

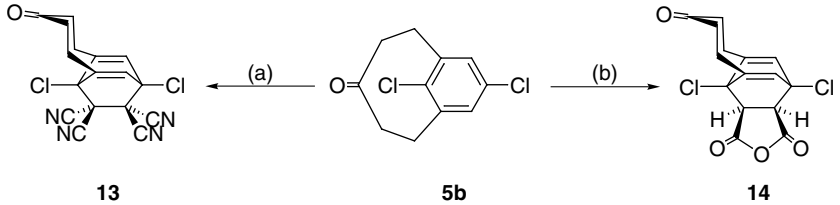
In contrast, in the IR spectrum, the CO stretching frequency of **5b** deviates strongly from the typical values found for saturated cyclic ketones ($\leq$1700 cm^{-1}).[32,33] The decreased stretching frequency (1674 cm^{-1}) in KBr seems to indicate a weakening of the CO bond in **5b**. This is not completely unprecedented, as Inazu et al. reported values of 1687–1689 cm^{-1} for several paracyclophanone derivatives.[34] However, for metacyclophanones, values are usually between 1700 and 1715 cm^{-1}.[26,33] As the interatomic distance between C(3) and C(11) is only 2.676 Å, which is less than the sum of the van der Waals radii (3.85 Å),[35] the possibility of electronic intra-annular through-space interactions may be considered. When the IR spectrum of **5b** was measured in solution ($CDCl_3$), two partially overlapping vibration frequencies were observed at 1680 and 1693 cm^{-1}, the latter being the predominant one. Although a comparison of the CO stretching frequencies of the propellane **11** in KBr (at 1698 cm^{-1}) and in $CDCl_3$ (at 1701 cm^{-1}; Table 2) shows that, in solution, a small shift towards higher wave numbers occurs, this effect cannot account for the relatively strong shift in the case of **5b**. A rationalisation of the observed decrease in the CO stretching frequency of **5b** in KBr is the possibility of dipole interactions in the solid state, which weaken the carbonyl bond. However, there may exist an electronic interaction between the carbonyl group and the aromatic ring in solution as both observed stretching frequencies are smaller than 1700 cm^{-1}. An electronic effect is also observed in the UV spectrum of **5b**. If one compares the first three electronic transitions of **1b** (235, 271, 325 nm) and **5b** (238, 284, 345 nm) in ethanol, it is evident that the spectrum of **5b** shows a bathochromic shift. The implications of these results will be further dealt with in the discussion (vide infra).

2.4. Reactivity of 5b

In a preliminary investigation, the reactivity of **5b** towards dienophiles and acid was studied. Although the angular and the torsional strain in the bridge of **5b** are reduced, the deformation of its benzene ring is comparable to that of **1b**; this is analogous to what was found for azacyclophane **3b**.[13] Parallel to the decrease of strain in the bridge of **5b**, its reactivity decreases compared to that of **1b**, both towards dienophiles and towards acid.

Cyclophanone **5b** reacted with tetracyanoethylene (TCNE) or maleic anhydride (MA) at room temperature in $CDCl_3$ solution, though rather sluggishly, to give the adducts **13** and **14**, respectively (Scheme 2).

In competition experiments, in which a dienophile was added to a 1:1 mixture of **5b** and azacyclophane **3b** in $CDCl_3$, **5b** displayed a decreased reactivity compared to **3b** (Table 3), which might be ascribed to the higher degree of distortion of the benzene ring of **3b** compared to that of **5b**. However, when the same type of experiment was performed with a 1:1 mixture of **5b** and **1b** in $CDCl_3$, cyclophane **1b** reacted much faster than **5b**. The experiments with TCNE were performed with an excess of dienophile (4 equiv.; Table 3, entry 1), as well as by adding small portions of a dilute solution of TCNE in $CDCl_3$ (Table 3, entry 2). As expected, the product ratio changed in favour of the less reactive species when an excess of the dienophile was used; however, the general trend remained the same. In the reaction with MA, the product ratio was less pronounced



Scheme 2. (a) TCNE, $CDCl_3$, rt; (b) MA, $CDCl_3$, rt.

Table 3. Ratio of addition products obtained with Diels–Alder reagents from 1:1 mixtures of **1b** and **5b**, or **3b** and **5b**, respectively

Reagent	Substrate mixture	
	1b/5b	**3b/5b**
TCNE	5.5:1	2:1
TCNE	10:1	2.5:1
MA	3:1	1:1

than in the case of TCNE (Table 3, entry 3). Because of the low solubility of **14** in $CDCl_3$, the calculated ratio in this case was based on the consumption of the reactants. The increased reactivity of **5b** towards MA is expressed in the competition reactions with both **1b** and **3b**. The results of the Diels–Alder reactions indicate that cyclophanone **5b** possesses a reactivity which is intermediate between that of azacyclophane **3b**[13] and silacyclophane **2b**;[15] the latter was completely unreactive towards TCNE or MA.

The 3-methylene analogue **1b** undergoes acid catalysed rearrangements to its *ortho*-isomer when exposed to low concentrations of trifluoroacetic acid (TFA).[5,8] When a catalytic amount of TFA was added to a $CDCl_3$ solution of **5b**, the ^{1}H NMR signals of the cyclophanone decreased very slowly. Yet apart from broad signals indicative of the formation of polymer, the signals of the expected *ortho*-isomer were not observed. When a 1:1 mixture of **1b** and **5b** in $CDCl_3$ was exposed to TFA, the ^{1}H NMR signal intensities of **1b** decreased considerably faster than those of **5b**. Thus, also towards acid, **1b** appears to be more reactive than the cyclophanone.

3. Calculations and discussion

The results from the X-ray crystal structure determination and the reactivity studies suggest that, contrary to what we had assumed previously,[18] the reactivity of the [5]metacyclophane system is not exclusively dependent on the degree of deformation of the benzene ring. [5]Metacyclophanes with a comparable deformation of the benzene rings display a considerable difference in reactivity towards various reagents. On the other hand, there is a trend that decreased reactivity roughly goes along with a decrease of the strain in the bridge due to incorporation of an sp^2-centre. Recently, we have demonstrated by extensive DFT calculations that incorporation of sp^2-hybridised carbon atoms in the bridge of a [5]metacyclophane has a small influence only, because the increase of the SE due to the shorter bridge length is counterbalanced by a reduction of the angular and torsional strain.[17] For **5b**-*exo*, these calculations predicted a reduction of the strain in the bridge (SE (br) (**1b**-*exo*)−SE (br) (**5b**-*exo*)=10.6 kJ mol^{-1}); this has now been confirmed by its crystal structure data (vide supra). However, the overall SE of **5b**-*exo* (186.8 kJ mol^{-1}) is even slightly larger than the SE calculated for **1b**-*exo* and **4b**-*endo* due to a larger repulsion between the bridge and the benzene ring. As has been demonstrated previously, the DFT calculated geometries are in good agreement with the X-ray data. The same holds for the geometries calculated at the B3LYP/6-31G*[36,37] level of theory reported in Table 4.

Table 4. Calculations (B3LYP/6-31G*) on **1b** and **5b**; selected bond lengths (Å) and angles (deg); X-ray values in brackets

	1b-*exo*	**1b**-*endo*	**5b**-*exo*	**5b**-*endo*
C(1)–C(2)	1.574 [1.569]	1.589	1.576	1.590 [1.578]
C(2)–X(3)	1.574 [1.566]	1.577	1.564	1.563 [1.547]
C(1)–C(10)	1.511 [1.506]	1.512	1.516	1.518 [1.516]
C(6)–C(7)	1.402 [1.400]	1.401	1.402	1.399 [1.396]
C(7)–C(8)	1.396 [1.389]	1.396	1.397	1.396 [1.388]
C(10)–C(11)	1.397 [1.391]	1.396	1.399	1.398 [1.390]
C(10)–C(1)–C(2)	105.9 [104.7]	109.01	105.40	108.18 [107.28]
C(1)–C(2)–X(3)	122.0 [121.9]	120.57	118.56	115.95 [115.73]
C(2)–X(3)–C(4)	123.0 [122.2]	120.37	122.52	121.16 [120.65]
α	27.4 [26.8]	27.0	27.1	26.5 [26.6]
β	48.2 [48.0]	46.2	48.0	46.9 [46.3]
γ	11.2 [12.0]	10.7	11.2	11.0 [11.9]

This high degree of accuracy gives confidence that the same holds for the conformers for which X-ray data are not available. The calculated bond lengths are slightly overestimated, as are the bond angles at C(1) and X(3). The total deformation of the benzene rings of **1b** and **5b** is very similar; in both cases, the benzene ring is less distorted in the *endo*-conformation. Both **1b** and **5b** are highly similar in the *exo*-conformation, which is the most stable conformer both according to calculation (ΔE_{tot} **1b**=−8.6 kJ mol^{-1}, ΔE_{tot} **5b**=−6.8 kJ mol^{-1}) and to ^{1}H NMR measurements in solution ($\Delta\Delta H^0$ **1b**=−3.05 kJ mol^{-1}, $\Delta\Delta H^0$ **5b**=−3.14 kJ mol^{-1}). This compares well with the differences obtained by previous DFT calculations (ΔE_{tot} **1b**=−7.3 kJ mol^{-1}, ΔE_{tot} **5b**=−5.8 kJ mol^{-1}).[17]

Incorporation of a carbonyl group in the bridge of a [5]metacyclophane lowers the energy of the Frontier Molecular Orbitals (FMO). In the two possible conformations, both the energy of the LUMO and of the HOMO of **5b** are lower than those of **1b**. The value of (ΔHOMO **1b**)−(ΔHOMO **5b**) is 0.266 eV (25.7 kJ mol^{-1}) for the *exo*-conformer and 0.175 eV (16.9 kJ mol^{-1}) for the *endo*-conformer, which may in part account for the observed reduced reactivity of **5b**. In contrast to our expectations from the IR and UV spectroscopic results (vide supra), the HOMO of **5b** shows no interaction between the benzene ring and the carbonyl group, neither in the *exo*- nor in the *endo*-conformation. However, the HOMO(−1) and the HOMO(−2) do show an interaction between the π-system of the benzene ring and one of the lone pair orbitals at oxygen (which is orthogonal to the CO π-system) via the σ-frame of the bridge, but there is no π–π interaction between the benzene ring and the carbonyl group, neither through-bond nor through-space. For **1b** a similar, yet less pronounced, interaction between the benzene ring π-system and the σ-frame of the bridge was found. Although surprising at first sight, these results are in fact quite similar to those reported by Gleiter et al. for several types of stelladiones and stellenones.[38,39]

This leads to the conclusion that the observed differences in reactivity of **1b** and **5b** are not caused by a decrease in electron density on the aromatic ring of **5b** as a result of π–π interaction and electron withdrawal by the carbonyl group. In order to fully comprehend the effects and the nature of the π–σ interactions in the HOMO(−1) and the HOMO(−2) of **5b**, a more rigorous theoretical analysis

is required, which was beyond the scope of the present investigation.

Whereas the ab initio results cannot fully explain the IR spectroscopy results, the observed bathochromic shift in the UV spectrum of **5b** can be rationalised based on the differences in the HOMO–LUMO gaps of **1b** and **5b**. The calculated difference of 0.276 eV (26.6 kJ mol^{-1}) is equivalent to a red shift of 25 nm, which is in rather good agreement with the observed red shift of 20 nm.

4. Conclusions

Although there are rough correlations between the length of the bridge of an [*n*]metacyclophane (*n*=5, 6, 7), the degree of bending of the benzene ring, the strain energy of the cyclophane, and its reactivity, these relationships are not clear-cut when a series of [5]metacylophane derivatives with sp^2-hybridised carbon atoms in the bridge are considered. Studies of the properties of **5b** confirmed our previous calculational predictions that the introduction of sp^2-hybridised carbon atoms in the bridge has a minute influence only on the structure and strain energy of a [5]metacyclophane.

A close examination of **5b** by B3LYP/6-31G* calculations revealed that the intramolecular electronic interactions are more intricate than expected. An interaction between the π-systems of the carbonyl group and the benzene ring, which was at first believed to be the cause of the observed red shift in the IR spectrum, was not confirmed by these calculations. Instead, orbital interactions between the π-system of the benzene ring and the lone pair at oxygen via the σ-frame of the bridge were found.

The curious fact remains that, despite a decrease in strain in the bridge of **5b** (as well as of azacyclophane **3b**) compared to the parent compound **1b**, the deviation angle α is not reduced. Yet, **5b** displays a reduced reactivity in Diels–Alder reactions. Thus, there appears to be no linear relationship between the total deformation of the benzene ring and its reactivity, in contrast to our earlier assumptions. Although in the case of **5b**, it cannot be ruled out that the reduced reactivity originates in part from the lowered energy of the HOMO, we believe that the pronounced differences in reactivity are caused by differences in the release of strain in the addition reactions, which according to the Hammond postulate will to some extent be reflected in the transition state.

5. Experimental

5.1. General

^{1}H NMR spectra were recorded at 200.13 MHz (Bruker AC 200) or at 400.13 MHz (Bruker MSL 400). ^{13}C NMR spectra were recorded at 50.32 MHz (Bruker AC 200) or at 100.62 MHz (Bruker MSL 400). The assignment of NMR signals is based on HH-COSY, CH-correlation, and NOE experiments. HRMS spectra were recorded on a Finnigan MAT-90 mass spectrometer operating at an ionisation potential of 70 eV. GC–MS spectra were recorded on a Hewlett–Packard 5971 series mass selective detector. Sample separation for GC–MS was performed on a Hewlett–Packard 5890 series II gas chromatograph fitted with an HP-1 column (50 m, 0.2 mm i.d., 0.33 mm film thickness). IR spectra were recorded on a Mattson Instruments 6030 Galaxy Series FT-IR spectrometer. UV spectra were recorded on a Cary 1 Bio UV–Vis spectrophotometer. Aluminium oxide used: Merck, Aluminium oxide 90, standardised (activity II–III), 0.063–0.200 mm. Silica gel used: Riedel-de Haën, Silica gel S, 0.2–0.5 mm. All chemicals used were commercially available from either Acros or Aldrich Chemicals.

5.2. Calculational details

The B3LYP/6-31G*[36,37] calculations were carried out with the GAUSSIAN94 suite of programs.[40]

5.2.1. 2,3-Bis(2-bromoethyl)butadiene (7). To a solution of **6**[13] (14.86 g, 33 mmol) in acetone (400 mL, anhydrous), LiBr (30.24 g, 348 mmol, anhydrous) was added under nitrogen. The reaction mixture was stirred under reflux for 6 h. Afterwards the solvent was removed under reduced pressure. To the residue water was added, and the organic layer was separated. The water layer was extracted with pentane (3×), and the combined organic layers were washed with water (4×) and brine (1×) and dried ($MgSO_4$), after which the solvent was removed under reduced pressure, yielding 7.78 g (29 mmol, 88%) of **7** as a slightly yellow oil. Further purification was achieved by column chromatography (Al_2O_3, pentane), followed by recrystallisation from pentane at −20°C; mp <−10°C. ^{1}H NMR ($CDCl_3$): δ 5.21 (s, 2H), δ 5.11 (s, 2H), δ 3.45 (t, *J*=7.5 Hz, 4H), δ 2.81 (t, *J*=7.5 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 142.9 (s), δ 114.7 (t, *J*=157 Hz), δ 37.6 (t, *J*=129 Hz), δ 31.1 (t, *J*=152 Hz); HRMS ($C_8H_{12}{}^{79}Br_2$), calcd 265.9306, observed 265.9305±0.0007.

5.2.2. 1-(2-Bromoethyl)-1-[1-(2-bromoethyl)-vinyl]-2,2-dichlorocyclopropane (8). To a solution of 1.28 g (4.8 mmol) of **7** and 3.9 mL (48 mmol) of $CHCl_3$ (dry) in pentane (20 mL, dry), 6.41 g (57 mmol) of *t*-BuOK was added via a solid reagent addition tube during a period of 0.5 h under nitrogen. After the addition was complete, the reaction mixture was stirred for another 4 h at room temperature. Afterwards the brown suspension was poured into ice water, and the organic layer was separated. The water layer was extracted with pentane (2×), and the combined organic layers were subsequently washed with water (3×) and brine (1×) and dried ($MgSO_4$), after which the solvent was removed under reduced pressure, yielding 1.31 g (78%) of a brown oil. As the reaction mixture still contained ca. 33% of **7**, the sequence described above was repeated twice, which resulted in a final conversion of >98%. The final brown oil was purified by column chromatography (Al_2O_3, pentane), followed by recrystallisation from pentane at −20°C, giving a final yield of about 80% of **8** as colourless crystals; mp 38°C; ^{1}H NMR ($CDCl_3$): δ 5.24 (t, *J*=1.6 Hz, 1H), δ 5.17 (t, *J*=1.1 Hz, 1H), δ 3.58 (m, 2H), δ 3.38 (ABKL-system, δ_A=3.45, δ_B=3.30, J_{AB}=10.1 Hz, J_{AK}=8.3 Hz, J_{AL}=4.4 Hz, J_{BK}=8.4 Hz, J_{BL}=7.7 Hz, 2H), δ 2.76 (ABKL-system, δ_A=2.81,

δ_B=2.70, J_{AB}=16.8 Hz, J_{AK}=7.7 Hz, J_{BK}=8.3 Hz, 2H), δ 2.26 (ABKLX-system, δ_A=2.60, δ_B=1.92, J_{AB}=14.8 Hz, J_{AK}=7.7 Hz, J_{AL}=4.4 Hz, J_{AX}=1.6 Hz, J_{BK}=8.4 Hz, J_{BL}=8.4 Hz, 2H), δ 1.92 (ABX-system, δ_A=1.81, δ_B=1.62, J_{AB}=7.6 Hz, J_{AX}=1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 142.4 (s), δ 116.9 (t, J=158 Hz), δ 63.5 (s), δ 40.4 (s), δ 36.2 (t, J=123 Hz), δ 35.9 (t, J=135 Hz), δ 31.4 (t, J=160 Hz), δ 29.4 (t, J=150 Hz), δ 29.3 (t, J=148 Hz); HRMS ($C_9H_{12}{}^{79}Br_2{}^{35}Cl_2$), calcd 347.8683, observed 347.8684±0.0010; Anal. Calcd for $C_9H_{12}Br_2Cl_2$: C, 30.80; H, 3.45. Found: C, 30.91; H, 3.41.

5.2.3. 1,2-Bis-(2-bromoethyl)-4,4-dichlorocyclopentene (9). Compound **8** was pyrolysed under FVT conditions: pressure 5×10^{-5} mbar; preheating temperature 180°C; oven temperature 480°C.[20] The mass recovery was ca. 90%. Crude **9** was flushed out of the cold trap with $CHCl_3$, which immediately coloured purple. After evaporation of the solvent, the brown/purple crude **9** was purified by column chromatography (alumina, pentane/diethyl ether) to yield **9** as a slightly yellow oil. Further purification was achieved by recrystallisation from $CHCl_3$/pentane at −20°C, giving **9** as colourless crystals: mp 47–48°C; ^{1}H NMR ($CDCl_3$): δ 3.38 (t, J=7.0 Hz, 4H), δ 3.29 (s, 4H), δ 2.69 (t, J=7.0 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 133.6 (s), δ 87.6 (s), δ 57.3 (t), δ 31.1 (t), δ 29.7 (t); MS *m/z* (rel. intens., isotope composition) 348 (8, $M^{+\cdot}$, $^{35}Cl_2{}^{79}Br_2$), 313 (18, $^{35}Cl^{79}Br_2$), 312 (17), 268 (4, $^{35}Cl_2{}^{79}Br$), 233 (100, $^{35}Cl^{79}Br$); Anal. Calcd for $C_9H_{12}Br_2Cl_2$: C, 30.80; H, 3.45. Found: C, 30.89; H, 3.35.

5.2.4. 1,5-Bis-(2-bromoethyl)-3,3,6,6-tetrachlorobicyclo-[3.1.0]hexane (10). To a solution of **9** (3.55 g, 10.1 mmol) and *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide (5 mol%) in $CHCl_3$ (24.17 g, 20 equiv.), 7.28 g of a 50% (w/v) aqueous NaOH solution (18 equiv.) was added at 0°C. This reaction mixture was then violently stirred for 24 h at room temperature. Afterwards water was added and the organic layer was separated. The water layer was extracted with $CHCl_3$ (3×), and the combined organic layers were washed with water (2×) and brine (1×). Drying ($MgSO_4$) was followed by removal of the solvent under reduced pressure. NMR analysis of the crude residue revealed a quantitative conversion. The crude product (4.60 g) was purified by column chromatography (silica, pentane, pentane/diethyl ether), yielding **10** (3.60 g, 8.3 mmol, 83%). Recrystallisation from $CHCl_3$ at −20°C gave **10** as colourless crystals: mp 95–97°C; ^{1}H NMR ($CDCl_3$): δ 3.46 (ABKL-system, δ_A=3.49, δ_B=3.42, J_{AB}=10.0 Hz, J_{AK}=10.1 Hz, J_{AL}=6.0 Hz, J_{BK}=5.4 Hz, J_{BL}=10.2 Hz, 4H), δ 2.93 (AA′BB′-system, δ_A=3.02, δ_B=2.83, J_{AB}=15.2 Hz, $J_{AA'}$=3.2 Hz, 4H), δ 2.32 (ABKL-system, δ_A=2.41, δ_B=2.22, J_{AB}=14.4 Hz, J_{AK}=10.1 Hz, J_{AL}=5.4 Hz, J_{BK}=10.2 Hz, J_{BL}=6.0 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 91.5 (s), δ 75.0 (s), δ 53.8 (t, J=137 Hz), δ 43.9 (s), δ 33.5 (t, J=132 Hz), δ 27.4 (t, J=152 Hz, *C*H2Br); Anal. Calcd for $C_{10}H_{12}Br_2Cl_4$: C, 27.69; H, 2.79. Found: C, 28.13; H, 2.73.

5.2.5. 9,9,13,13-Tetrachlorotricyclo[5.3.1.0]undeca-4-one (11). A dispersion of NaH (2.5 equiv.) in mineral oil (60% w/w) was washed with anhydrous pentane (3×). Then diethyl ether/DMSO (50:50, 150 mL, dry) was added under nitrogen. To this suspension, TosMIC (2.93 g, 15.0 mmol) was added under stirring at 0°C under nitrogen. After the addition was complete, the resulting yellow suspension was stirred for 1 h at rt. Afterwards the suspension had turned dark brown, and a solution of **10** (6.50 g, 15.0 mmol) in DMSO/diethyl ether (50:50, 30 mL, dry) was added slowly. After stirring for 12 h at rt, water was added carefully to the dark brown solution to remove the excess of NaH. When the evolution of hydrogen gas had stopped, the solution was poured into water, and the water layer was extracted with diethyl ether (3×). The combined organic layers were washed with water (5×) and brine (1×), and dried ($MgSO_4$). After evaporating 90% of the solvent under reduced pressure, CH_2Cl_2 was added to the residue. Then several mL of concentrated aqueous HCl were added slowly, and the mixture was stirred for 20 min. Afterwards, water was added and the water layer was extracted with $CHCl_3$ (3×). The combined organic layers were washed with aqueous 2N $NaHCO_3$ (2×), water (3×) and brine (1×), and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave crude **11** as a brown solid. Purification was achieved by column chromatography (alumina, pentane/ethyl acetate 90:10), followed by recrystallisation from $CHCl_3$, to give **11** in an isolated yield of 15–20%.

11. Mp 162–164°C; IR (CO): 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.46 (ABKL-system, δ_A=3.49, δ_B=3.42, J_{AB}=10.0 Hz, J_{AK}=10.0 Hz, J_{AL}=6.2 Hz, J_{BK}=10.0 Hz, J_{BL}=5.5 Hz, 4H), δ 2.92 (AA′BB′-system, δ_A=3.02, δ_B=2.83, J_{AB}=14.4 Hz, $J_{AA'}$=3.2 Hz, 4H), δ 2.32 (ABKL-system, δ_A=2.42, δ_B=2.23, J_{AB}=14.4 Hz, J_{AK}=10.0 Hz, J_{AL}=5.5 Hz, J_{BK}=10.0 Hz, J_{BL}=6.2 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ 210.39 (s, CO), δ 91.4 (s, C_9), δ 77.1 (s, C_{11}), δ 58.8 (t, J=137 Hz, $C_{8/10}$), δ 43.2 (s, $C_{1/7}$), δ 41.2 (t, J=129 Hz, $C_{3/5}$), δ 24.6 (t, J=129 Hz, $C_{2/6}$); MS *m/z* (rel. intens., isotope composition) 300 (17, $M^{+\cdot}$, $^{35}Cl_4$), 265 (23, $^{35}Cl_3$), 230 (75, $^{35}Cl_2$), 229 (41, $^{35}Cl_2$), 159 (45), 55 (100); Anal. Calcd for $C_{11}H_{12}OCl_4$: C, 43.74; H, 4.01. Found: C, 43.70; H, 3.99.

5.2.6. 8,11-Dichloro[5]metacyclophan-3-one (5b). A solution of $AgClO_4$ (1.68 g, 6 equiv.), lutidine (0.42 g, 3 equiv., dry) and **11** (0.41 g, 1.35 mmol) in THF (15 mL) was stirred for 60 h under nitrogen. Afterwards saturated NaCl solution was added to the reaction mixture, and this mixture was filtered through a glass filter. To the filtrate, water was added, and the water layer was extracted with $CHCl_3$ (3×). The combined organic layers were washed with brine (1×) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure yielded crude **5b**. Purification was achieved by column chromatography (alumina, pentane/ethyl acetate 90:10), followed by recrystallisation from CH_2Cl_2, to give **5b** in an isolated yield of 277 mg (90%).

5b. Mp 156–159°C; IR (CO): 1674 cm^{-1}; UV–Vis (EtOH): λ_{max}=206.4, 220.1, 237.9, 284.3, 345 nm; ^{1}H NMR ($CDCl_3$, 210 K, *exo*-conformer): δ 6.96 (s, 2H), δ 3.27 (ABKL-system, δ_A=4.06, δ_B=2.48, J_{AB}=13.0 Hz, J_{AK}=12.6 Hz, J_{AL}=3.2 Hz, J_{BK}=4.6 Hz, J_{BL}=3.1 Hz, 4H), δ 2.19 (ABKL-system, δ_A=2.27, δ_B=2.08, J_{AB}=11.3 Hz, J_{AK}=3.2 Hz, J_{AL}=3.1 Hz, J_{BK}=12.6 Hz, J_{BL}=4.6 Hz, 4H); ^{1}H

Table 5. Crystal data and details of the structure determination for **5b**

Crystal data			
Empirical formula			$C_{11}H_{10}Cl_2O$
Formula weight			229.11
Crystal system			Orthorhombic
Space group		*Pnma*	(No. 62)
a, *b*, *c* (Å)	8.0830 (11)	9.0329 (5)	13.3408 (14)
V (Å^3)			974.05 (18)
Z			4
D(calc) (g/cm^3)			1.562
F(000)			472
Mu (MoKα) (cm^{-1})			6.2
Crystal size (mm)			0.25×0.30×0.50
Data collection			
Temperature (K)			293
Radiation (Å)		MoKα	0.71073
Theta, Min.–max. (deg)		2.7	27.5
Tot., Uniq. Data, *R* (int)	2369	1185	0.027
Observed data [$I>2.0\sigma(I)$]			1034
Refinement			
N_{ref}, N_{par}		1185	74
R, ωR_2, *S*	0.0366	0.0990	1.04
Max. and Av. shift/error		0.00	0.00
Min. and max. resd. dens. (e/Å^3)		−0.65	0.28

NMR ($CDCl_3$, 210 K, *endo*-conformer): δ 6.77 (s, 2H), δ 3.21 (ABKL-system, δ_A=3.77, δ_B=2.64, J_{AB}=14.2 Hz, J_{AK}=10.2 Hz, J_{AL}=1.3 Hz, J_{BK}=10.4 Hz, J_{BL}=7.3 Hz, 4H), δ 3.08 (ABKL-system, δ_A=3.93, δ_B=2.22, J_{AB}=12.6 Hz, J_{AK}=10.2 Hz, J_{AL}=7.3 Hz, J_{BK}=10.4 Hz, J_{BL}=1.3 Hz, 4H); ^{13}C NMR ($CDCl_3$, 218 K, *exo*-conformer): δ 214.1 (s, C_3), δ 146.7 (s, $C_{6/10}$), δ 140.9 (s, C_{11}), δ 134.4 (s, C_8), δ 123.4 (d, *J*=169 Hz, $C_{7/9}$), δ 52.6 (t, *J*=130 Hz, $C_{2/4}$), δ 36.0 (t, *J*=136 Hz, $C_{1/5}$); ^{13}C NMR ($CDCl_3$, 218 K, *endo*-conformer): δ 210.6 (s, C_3), δ 146.6 (s, $C_{6/10}$), δ 144.1 (s, C_{11}), δ 132.3 (s, C_8), δ 125.8 (d, *J*=170 Hz, $C_{7/9}$), δ 43.2 (t, *J*=131 Hz, $C_{2/4}$), δ 33.8 (t, *J*=134 Hz, $C_{1/5}$); MS *m*/*z* (rel. intens., isotope composition) 228 (36, $M^{+\cdot}$, $^{35}Cl_2$), 193 (100, ^{35}Cl), 165 (51), 151 (71), 115 (67); Anal. Calcd for $C_{11}H_{10}Cl_2$: C, 57.67; H, 4.40; Cl, 30.95. Found: C, 57.39; H, 4.45; Cl, 31.50 (Table 5).

X-Ray structure determination of ***5b***. X-Ray data were collected on an Enraf–Nonius CAD4F/Rotating Anode diffractometer for a 'cut-to-size' crystal at room temperature. The structure was solved by Direct Methods using SHELXS97[41] and refined on F^2 by full matrix least squares using SHELXL97.[42] Hydrogen atoms were introduced at calculated positions and included in the refinement riding on their carrier atoms. Full details have been deposited at the Cambridge Crystallographic Data Centre (CCDC-149572).

5.2.7. 1,10-Dichloro-11,11,12,12-tetracyanotricyclo-[7.3.1.03,10]trideca-2,9(13)-dien-6-one (13). To an NMR solution of **5b** in $CDCl_3$, solid tetracyanoethylene (TCNE, excess) was added. The resulting dispersion turned slightly yellow. After 18 h the ^{1}H NMR signals of **5b** had disappeared, showing only the signals of **13**. The dispersion was filtered to remove the excess of solid TCNE. After evaporating the solvent from the filtrate, the resulting brownish solid was washed with diethyl ether to remove impurities, leaving a slightly yellow solid. GC–MS data of **13** could not be obtained as it underwent a thermal retro-Diels–Alder reaction in the injector of the GC. Furthermore it proved to be impossible to remove the excess of TCNE completely, which thwarted our attempts to obtain an elemental analysis.

13. ^{1}H NMR ($CDCl_3$, rt): δ 6.65 (s, 2H), δ 3.99 (ABKL-system, δ_A=3.20, δ_B=2.79, J_{AB}=13.8 Hz, J_{AK}=10.4 Hz, J_{AL}=4.8 Hz, J_{BK}=5.7 Hz, J_{BL}=5.2 Hz, 4H), δ 2.67 (ABKL-system, δ_A=2.88, δ_B=2.45, J_{AB}=10.8 Hz, J_{AK}=5.2 Hz, J_{AL}=4.8 Hz, J_{BK}=10.4 Hz, J_{BL}=5.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, rt): δ 210.48 (s, C(6)), δ 154.50 (s, C(3/9), δ 133.63 (d, C(2/13)), δ 111.78 (s, C(CN)), δ 109.80 (s, C(CN)), δ 109.66 (s, C(CN)), δ 107.70 (s, C(CN)), δ 75.81 (s, C(1) or C(10)), δ 66.75 (s, C(1) or C(10)), δ 55.19 (s, C(11) or C(12)), δ 53.78 (s, C(11) or C(12)), δ 47.63 (t, C(5/7) or C(4/8), δ 29.96 (t, C(5/7) or C(4/8)).

5.2.8. 2,11-Dichloro-14-oxatetracyclo[10.3.1^{3,11}.0.0^{2,9}]-pentadeca-3(16),9-dien-6,13,15-trione (14). To an NMR solution of **5b** in $CDCl_3$, a dilute solution of maleic anhydride (MA) in $CDCl_3$ was added. Addition was terminated when **5b** had been consumed (^{1}H NMR). During the reaction **14** precipitated from the solution. GC–MS data of **14** could not be obtained as it underwent a thermal retro-Diels–Alder reaction in the injector of the GC.

14. ^{1}H NMR ($CDCl_3$, rt): δ 6.64 (s, 1H), δ 6.41 (s, 1H), δ 3.70 (s, 2H), δ 3.40–2.42 (m, 8H); ^{1}H NMR (DMSO-d_6, rt): δ 6.67 (s, 1H), δ 6.57 (s, 1H), δ 3.88 (s, 2H), δ 2.90 (m, 1H), δ 2.71 (m, 1H), δ 2.60–2.48 (m, 4H), δ 2.45–2.37 (m, 2H); ^{13}C NMR (DMSO-d_6, rt): δ 212.53 (s, CO), δ 167.31 (s, CO), δ 166.76 (s, CO), δ 154.13 (s), δ 152.83 (s), δ 137.23 (d), δ 133.61 (d), δ 71.68 (s), δ 64.50 (s), δ 54.93 (d), δ 53.10 (d), δ 48.44 (t), δ 48.24 (t), δ 28.93 (t), δ 28.08 (t).

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