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New [4.4]Cyclophane Diketals, Monoketones, and Diketones: Design, Synthesis, and Structural Analysis

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The synthesis of some new [4.4]cyclophane diketals, monoketones, and diketones in good yields is reported along with the unusually low reactivity towards hydrolysis of the spiro-1,3-dioxane rings connected to the cyclophane bridges. The structural analysis carried out by X-ray diffraction, NMR spectroscopy, and mass spectrometry shows significant intra- and intermolecular π–π and C–H–π interactions. The rotation of the aromatic rings and the flipping of the bridges have been investigated by molecular modeling and variable-temperature NMR experiments.

Introduction

The properties of [4.4]cyclophanes[1] are somewhat between those of classic [2.2]cyclophanes and those of macrocycles with two (or more) aromatic rings which, formally, are considered as cyclophanes too. The aromatic units of [2.2]cyclophanes exhibit important interactions and the rotation of the aromatic rings is totally constrained, while macrocyclic cyclophanes show free or not completely hindered rotation of the aromatic groups.[2] The interactions between the aromatic parts in macrocyclic cyclophanes are weak, but sometimes they are responsible for the shape of the molecules in the solid state[3] and can determine the preference of the compounds for peculiar conformers in solution.[3a,4] Investigations of [4.4]cyclophanes have focused on the experimental and theoretical studies of the interactions between the aromatic rings[5] and on the conformational processes involved in the flipping of the bridges or the rotation of the aromatic units.[5,6] These conformational processes determine the equilibria between homomeric structures[6a,6b] or between different stereoisomers (*syn* and *anti* structures,[6c,6d] *like* and *unlike* isomers,[6e] conformers with different arrangements of the aromatic groups[6f–6h]). Some equilibria between cyclophanes with edge-to-face and face-to-face disposed aromatic rings can be controlled by electrochemical processes.[6i] The structural aspects of the [4.4]cyclophane series have mainly been revealed by NMR experiments[7] and single-crystal X-ray molecular structures.[5a,6a,6b]

Recently,[8] we reported the synthesis of [7.7]cyclophanes **i** and **ii** (Figure 1) starting from appropriate 1,3-dioxane derivatives of 1,4-diacetylbenzene and 2,6-diacetylpyridine. The substrates exhibit an axial orientation of the aromatic groups with respect to both 1,3-dioxane rings and a favorable arrangement (preorganization) of the reacting groups for high-yielding macrocyclization reactions. Encouraged by the previous results, we considered it of interest to use appropriate 1,3-dioxane derivatives of 1,4-diacetylbenzene in order to synthesize new dispiro diketal [4.4]cyclophanes **iii** (Figure 1) and the corresponding dioxocyclophanes and to investigate their structures and conformational behavior. The presence of 1,3-dioxane rings in **iii** is important, on the one hand, because the conformational behavior of the saturated heterocycles insures the required preorganization of the substrate for the closure of the macrocycle and, on the other hand, it facilitates the NMR investigation of the rotation of the aromatic groups. The methylene groups of the saturated heterocycles are differentiated (diastereotopic) in the NMR spectra if the rotation of the nonsymmetric aromatic ring (B) is hindered and they are rendered equivalent if the rotation of aromatic ring (B) is fast enough (e.g., in the case of the dynamic NMR investigations of some 2-aryl-2-methyl-1,3-dioxanes).[9]

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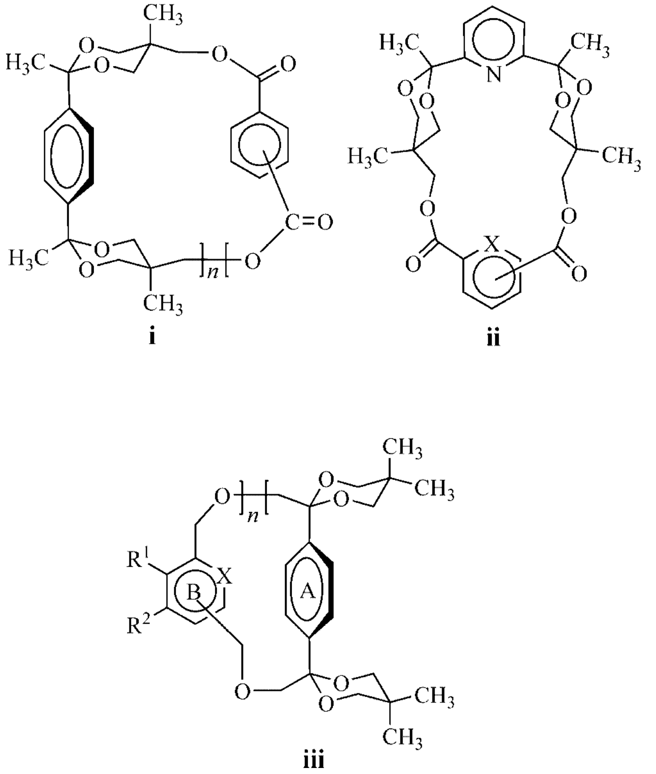
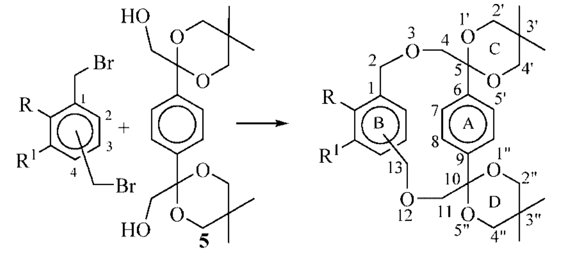


Figure 1. General formula of [7.7]cyclophanes **i** and **ii** and [4.4]-cyclophanes **iii** with 1,3-dioxane units.

Results and Discussion

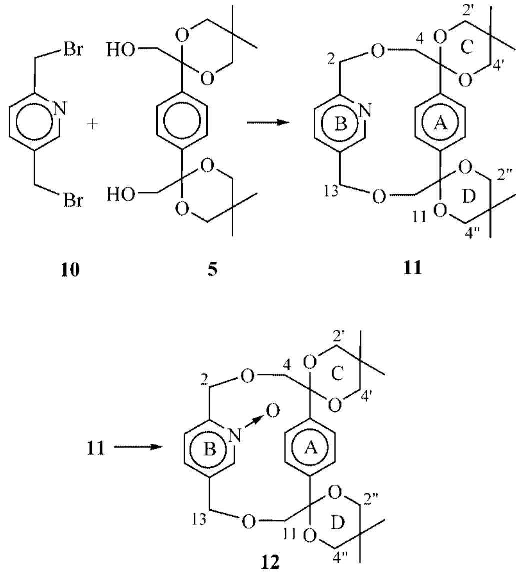
New [4.4]cyclophanes **6**–**9** and **11** were obtained (Schemes 1 and 2) in good yields (34–67 %) by the reaction of several bis(bromomethyl)arenes **1**–**4** and **10** with diol **5** using a typical procedure for the synthesis of macrocyclic ethers.[10] The 2,5-pyridinocyclophane **11** was transformed with *m*-CPBA, in good yields (83 %) into its *N*-oxide **12** (Scheme 2). The yields of the macrocyclization reactions are remarkable. The synthesis of [4.4]cyclophanes with sulfur atoms in the bridges (no diether [4.4]cyclophanes are reported), despite the anion of the mercapto derivatives being more reactive, has been achieved in similar or lower yields (10–72 %),[5a,11] and the reported yields for other macrocyclization reactions leading to the formation of cyclophanes by etherification reactions show in many cases lower values.[12] In order to access dioxocyclophanes, compounds **7**–**9** were submitted to deprotection reactions of the ketal groups (1,3-dioxane rings) using several methods. The usual deprotections with I_2 in acetone,[13] catalytic[14] or stoichiometric[15] amounts of cerium ammonium nitrate (CAN), or 6 N HCl[16] failed for **8**, but were successful in the cases of **7** and **9**, leading to the monoketones **13** and **14** (Scheme 3). All attempts to obtain (by the mentioned methods) the corresponding diketones starting from cyclophanes **7**–**9** or from the monoprotected derivatives **13** and **14** (even under harsh hydrolysis conditions: 6 N HCl in MeCN, 64 h at reflux) failed, and monoketones **13** and **14** or decomposition products were recovered. However, in the procedures with 6 N HCl or with stoichiometric amounts of CAN, the for-



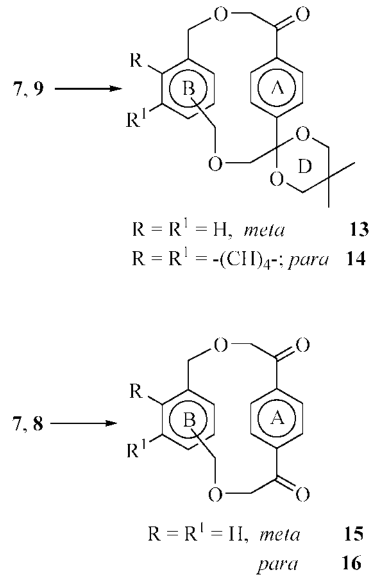
R = R1 = H, *ortho* **1**
meta **2**
para **3**
R = R1 = -(CH)4-; *para* **4**

R = R1 = H, *ortho* **6**
meta **7**
para **8**
R = R1 = -(CH)4-; *para* **9**

Scheme 1. Synthesis of **6**–**9**.



Scheme 2. Synthesis of **11** and **12**.



R = R1 = H, *meta* **13**
R = R1 = -(CH)4-; *para* **14**

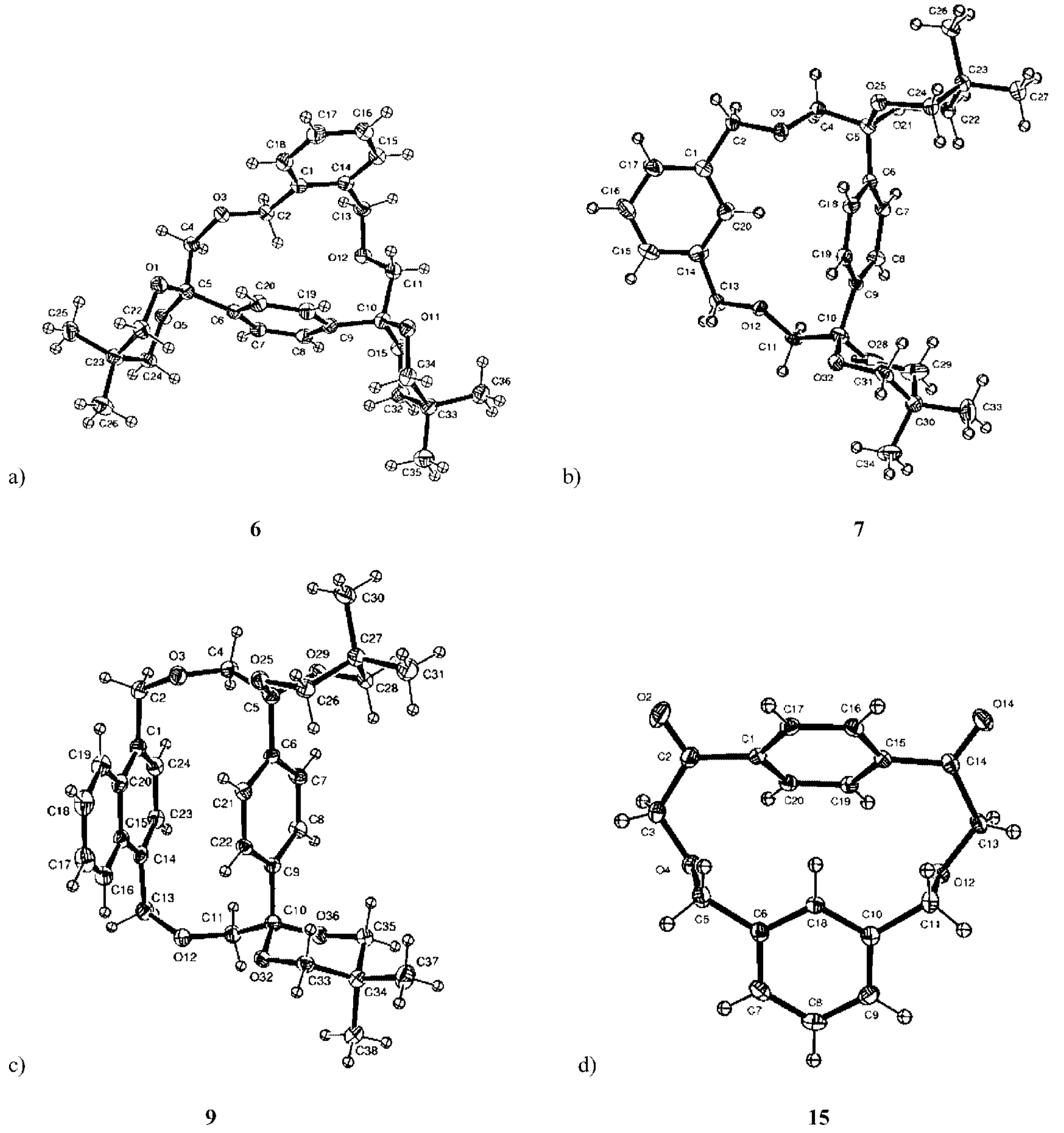
R = R1 = H, *meta* **15**
para **16**

Scheme 3. Synthesis of monoketones **13** and **14** and diketones **15** and **16**.

mation of small amounts of diketone **15** (Scheme 3) could be observed (NMR determined ratio of monoketone/diketone = 10:1). Surprisingly, the hydrolysis of **7** and **8** using a mixture of CAN (10 mol-%) and 6 N HCl (0.01 mL) was successful, giving good yields of diketones **15** and **16** which were isolated and characterized (Scheme 3). The dioxo[4.4]-cyclophanes are important targets in host molecule chemistry due to their ability to act as exocyclic receptors (e.g., for nucleic acids)[17] or they can be used as building blocks for further transformations. Despite the difficulties involved in the deprotection step, we obtained dioxo[4.4]cyclophanes **15** and **16** in total yields of 41 and 61 %, respectively. These values are considerably higher than the yields (5–18 %) reported for the direct macrocyclization method used to obtain other dioxo[4.4]cyclophanes[6c,6d,6g] (the strain in the target macrocycles due to the sp^2 hybridization of the carbonyl carbon atoms was considered responsible for the low yields).[6c]

Structural Aspects in the Solid State

The molecular structures of cyclophanes **6**, **7**, **9**, and **15** (Figure 2) were obtained by single-crystal X-ray diffractometry. The 1,4-phenylene ring exhibits an axial orientation with respect to both 1,3-dioxane rings (**6**, **7**, and **9**) and its deformation (measured by the angle between the bonds C5–C6 and C9–C10, Table 1) could be determined. The deformation angles decrease in the order *ortho*-phenylene > *meta*-phenylene > 1,4-naphthylene. The molecular structures show almost parallel orientation of rings A and B in **9**, face-tilted-to-face arrangement in **6**, and edge-tilted-



a) **6** b) **7**

c) **9** d) **15**

Figure 2. ORTEP diagrams for compounds **6** (a), **7** (b), **9** (c), and **15** (d).

Table 1. Relevant structural data calculated from the molecular structures of **6**, **7**, **9**, and **15**.

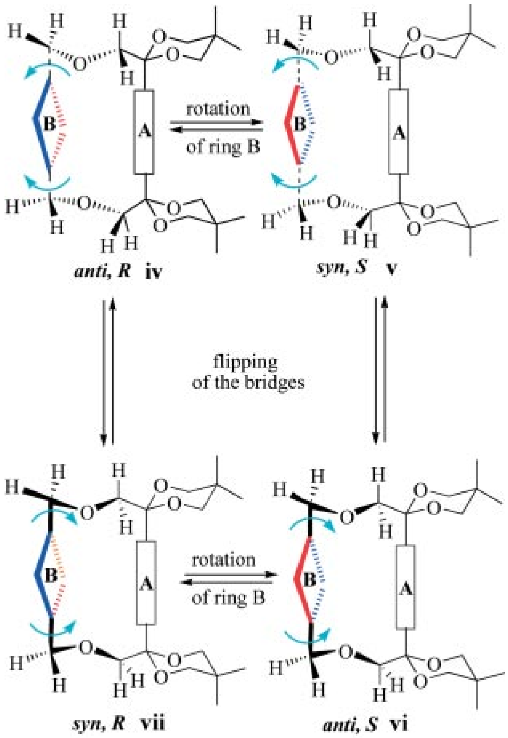
Compd.	a_1[a] [°]	d[b] [Å]	a_2[c] [°]	a_3[d] [°]	a_4[d] [°]
6	23.6	H2–A 2.499	30.0	84.2	84.3
7	57.4	H20–A 3.078	20.5	84.8	79.0 or 72.9
9	17.3	H21–B 3.292, H22–B 3.316	4.1	84.0	84.1
15	42.9	H18–A 2.617	7.6	–	–

[a] a_1 = angle between A and B. [b] Important distances for C–H–aromatic ring interactions, measured between the centers of the aromatic rings. [c] Deformation of ring B: a_2 = C5–C6/C9–C10. [d] Rotameric behavior of A: a_3 = A/C4–C5–C6, a_4 = A/C9–C10–C11; a_3 and a_4 exhibit values close to 0° for the bisectional rotamer of the 1,4-phenylene ring (A) and close to 90° for the orthogonal rotamer of this group.

to-face arrangement in compounds **7** and **15** (Table 1, Figure 2). The distances measured between some hydrogen atoms and the neighboring aromatic rings (Table 1) reveal C–H–π interactions (e.g., the distances between H20 in **7**, H18 in **15**, and H2 in **6** and the center of the aromatic ring A are 3.078, 2.617, and 2.499 Å, respectively). Investigation of the lattices of these compounds showed the assisted assembly of these molecules by C–H–π interactions (they are shown in the Supporting Information) which mainly involve the aromatic ring B and the hydrogen atoms belonging to the CH_2 groups of the bridges, the CH_3 groups at positions 5′ and 5′′ of the spiro-heterocycles, or the other aromatic ring A.

Structural Aspects in Solution

The structural investigations in solution of the diketal and monoketal [4.4]cyclophanes were carried out by performing complex NMR experiments and were focused on the conformational preferences of the dioxacyclohexane[18] rings (C and D, Schemes 1 and 2), on the rotameric behavior of the aromatic components (A and B) of the cyclophanes, and on the flipping equilibria of the bridges (Scheme 4). The rotation of the aromatic rings A and B and the flipping of the bridges (Scheme 4) can be monitored by variable-temperature NMR experiments. These conformational equilibria involve homomeric structures if ring B is symmetric or diastereoisomers if ring B is nonsymmetric. If the part of the nonsymmetric B ring of highest precedence (let us say that it is the one drawn in red in Scheme 4) is close to the center of ring A, the diastereomer is denoted as *syn* [enantiomeric structures **v** and **vii** in Scheme 4 (the planar chiral configuration is inverted due to the rotation of ring B)] and if this reference ring B is at a distance from ring A, then the corresponding diastereoisomer is denoted as *anti* (enantiomeric structures **iv** and **vi**, Scheme 4). The rotation of ring B, as well as the flipping of the chains, leads to an equilibration of the *syn* and *anti* structures. The *syn* and *anti* diastereoisomers can be observed by NMR only if both conformational equilibria are frozen. Rotation of ring B (which changes the planar chiral configuration) renders equivalent the CH_2 groups of the 1,3-dioxane rings and the protons of the same CH_2 group of the chains. The freezing of the rotation of ring B leads as a consequence to more complicated NMR spectra with different signals for the protons at the diastereotopic positions 2′(2′′) and 4′(4′′) of the dioxacyclohexane units and AB patterns for the protons of the same CH_2 group in the bridges. Further freezing of the flipping of the bridges determines (if the rotation of ring B is already blocked) the recording of two sets of signals (of different intensities) in the NMR spectra belonging to the *syn* and *anti* frozen diastereoisomers. Due to these particularities in the NMR spectra and to the fact that the barrier for the flipping of the bridges is lower than the barrier for the rotation of the aromatic rings, the conformational equilibria of the [4.4]cyclophanes can be, step by step, monitored by dynamic NMR experiments. In order to observe the conformational behavior of [4.4]cyclophanes, we carried out variable-temperature NMR measurements with compounds **6**, **7**, **9**, **11**, and **12**.



Scheme 4. Rotation of the nonsymmetric aromatic ring B and flipping of the bridges in [4.4]cyclophanes.

The room-temperature NMR investigations (^1H, ^{13}C, COSY, HMQC, HMBC, NOESY, and/or ROESY) reveal different signals for the axial and equatorial protons of the saturated heterocycles, while the NOESY or ROESY spectra show interactions between the signals of the aromatic

Table 2. NMR spectroscopic data ($CDCl_3$, 300 MHz) for **6**–**9** and **11**–**16**.

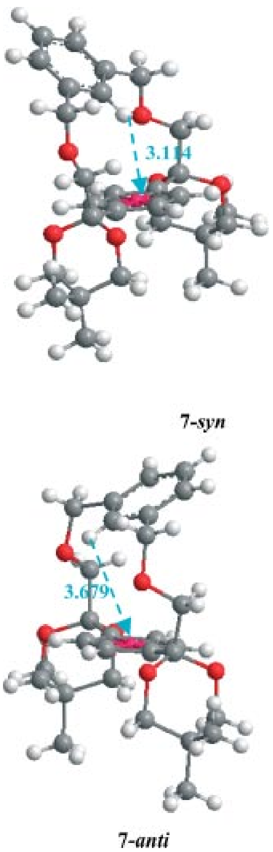
	δ [ppm]					
	H_{ax} 2′(2′′), 4′(4′′)	H_{eq} 2′(2′′), 4′(4′′)	4-CH*H*	11-CH*H*	2-CH*H*	13-CH*H*
6	3.51	3.72	3.46		3.53	
7	3.47	3.63	3.57		4.30	
8	3.31	3.37	3.78		4.27	
9	3.09, 3.14	3.26, 3.32	3.52, 4.22		4.09, 5.44	
11	3.33–3.43[a]		4.02, 4.11	3.49, 3.89	4.27, 4.50	4.10, 4.49
12	3.23–3.39[a]		4.02, 4.49	3.65, 3.87	4.10, 5.25	4.13, 4.28
13	3.49	3.59	5.53	3.56	4.34	4.11
14	3.16, 3.22	3.30, 3.37	4.70, 5.37	3.49, 4.10	4.57, 4.75	4.06, 5.33
15	–	–	4.54		4.14	
16	–	–	4.40		4.49	

[a] Overlapped peaks.

protons of ring A and the signals of the axial protons of the 1,3-dioxane units. These NMR spectroscopic data demonstrate the anancomeric structure of the dioxacyclohexane rings in all the investigated derivatives and the axial-orthogonal orientation of the 1,4-phenylene ring (A) with respect to both heterocycles in **6**–**9**, **11**, and **12** and with respect to the remaining heterocycle in the monoketones **13** and **14** (Table 2). The preference for these conformations is also predicted by molecular modeling (see the Supporting Information). Despite the previously shown similarities between the room-temperature NMR spectra of these compounds, their analysis revealed significant differences and two groups of diketal and monoketal [4.4]cyclophanes could be considered. The room-temperature NMR spectra of the first considered group (compounds **6**–**8** and **13**) do not differentiate the protons at positions 2′(2′′) and 4′(4′′) of the dioxacyclohexane rings or the protons of the same CH_2 group of the bridges. These results, obtained at room temperature, are supported by molecular modeling (calculated barriers lower than 10 kcal/mol) and suggest the fast flipping of the bridges in all these derivatives and the free rotation of the nonsymmetric aromatic ring B in compounds **7** and **13**.

Variable-temperature ^1H NMR experiments were carried out with **6** and **7**. The spectra ($CDCl_3$) of **7** run at lower (up to 210 K) and higher (up to 320 K) temperatures were not different to those recorded at room temperature. Molecular modeling of this compound showed that the rotation of ring B and the inversion of the chains are simultaneous. The calculated barrier, as expected, is very low [5.16 kcal/mol (PM3), 1.41 kcal/mol (B3LYP)]. The compound exhibits a preference for the *syn* structure (Figure 3) which corresponds to the edge-tilted-to-face arrangement of the aromatic rings (calculated $\Delta G_{anti\text{–}syn}$ = 0.89 kcal/mol). The preference for these structures is also supported by the shielding of the signal belonging to the proton at position 20 ($\delta_{(20\text{-H})}$ = 6.28 ppm). The fast conformational equilibrium for **7** is also suggested by literature data[6c,6d] which reveal low barriers for the flipping of the bridges in [4.4]-metaparacyclophanes.

Molecular modeling predicts for **6** a stable structure, similar to that observed in the solid state, which shows a torsion of the bridges in which one of the hydrogen atoms of one of the bridges can interact (C–H–π) with the aromatic ring A (see the Supporting Information). The room-temperature NMR spectrum (Figure 4) shows that the four protons at positions 2 and 13 are rendered equivalent (as well as those at positions 4 and 11) by the conformational equilibria of compound **6** (Scheme 5). These equilibria occur between four equivalent structures (**viii**–**xi**) and require besides the flipping of the bridges (2), an inside–outside movement (1) of the α-CH_2 groups (ring B is taken as a reference). In order to observe the specific conformational equilibria, variable-temperature NMR experiments were carried out with **6** in CD_2Cl_2 (Figure 4) and in [D$_8$]THF



7-syn

7-anti

Figure 3. *syn* and *anti* isomers of **7** [the distances between C(20) and the centroid of A are 3.114 and 3.679 Å, respectively].

(see the Supporting Information). The modifications to the spectra are similar in the two solvents. In Figure 4 it can be observed that the coalescence of the signals belonging to the aromatic protons of ring A (δ_{298} = 7.39 ppm) occurs at 180 K. The coalescence of the signals of the protons of the same CH_2 group (δ_{298} = 3.47 and 3.68 ppm) of the bridges begins at 220 K, and at 180 K the signals are completely indistinguishable from the baseline. The modifications to the NMR spectra caused by decreasing the temperature prove the flipping of the chains, but the conformational equilibria for **6** could not be completely frozen until 180 K in CD_2Cl_2 or 168 K in [D$_8$]THF. In agreement with the results of the variable-temperature NMR experiments, molecular modeling of **6** showed a higher value for the barrier for the flipping of the bridges ($\Delta G^{\#}$ = 9.79 kcal/mol; for the inside–outside movement of the chains $\Delta G^{\#}$ = 4.71 kcal/mol) than for compound **7**. This difference is probably due to the stabilization of the ground-state structures involved in the flipping of the bridges of **6** by C–H–π interactions between the α-CH_2 groups and the 1,4-phenylene ring (A). This explanation is supported by the shielding of the signal of these protons in **6** ($CDCl_3$; $\delta_{2,13}$ = 3.53 ppm) as compared with the signal of the corresponding protons in the ^{1}H NMR spectrum of **7** ($CDCl_3$; $\delta_{2,13}$ = 4.30 ppm).

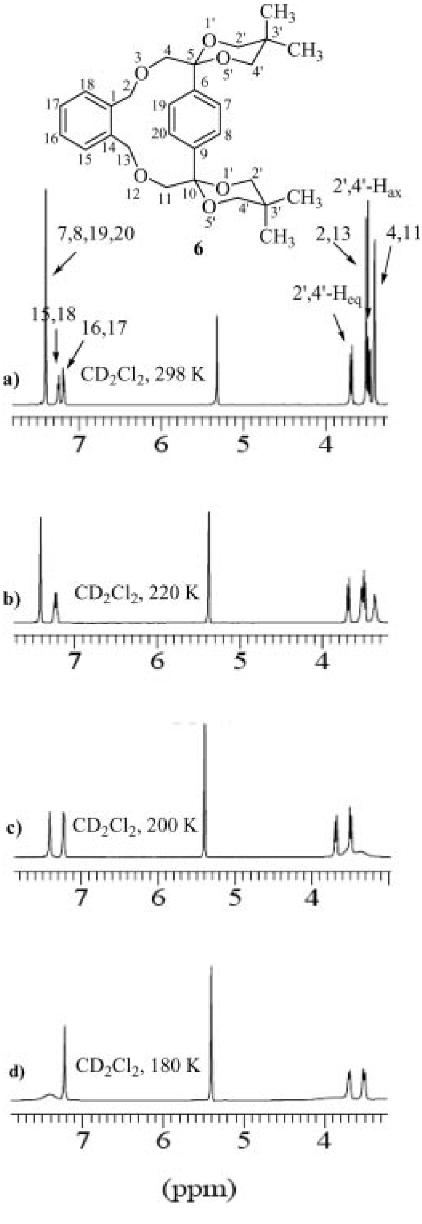
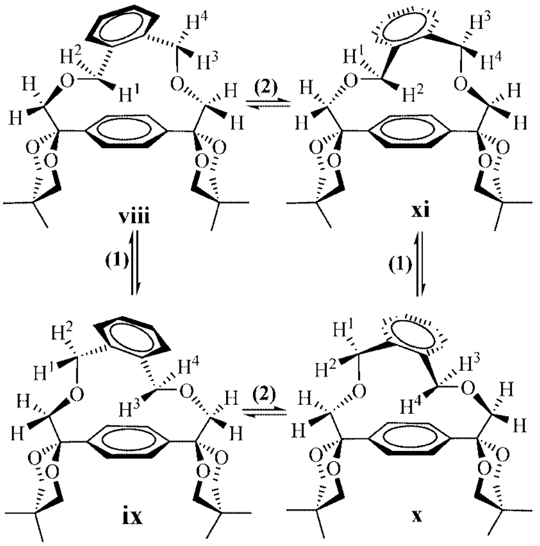


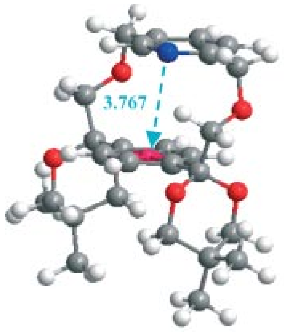
Figure 4. ^{1}H NMR spectra (500 MHz) of compound **6** in CD_2Cl_2 at 298 (a), 220 (b), 200 (c), and 180 K (d).



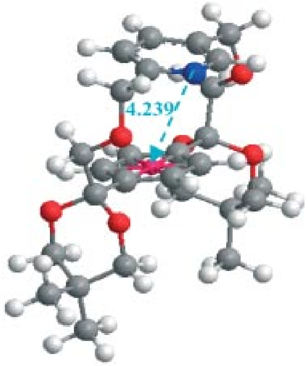
Scheme 5. Conformational equilibria for **6**.

For the second group of compounds (**9**, **11**, **12**, and **14**), the room-temperature ^{1}H NMR spectra exhibit different signals for the CH_2 groups [positions 2′(2′′) and 4′(4′′)] of the same dioxacyclohexane ring and for the protons of the same CH_2 group of the chains. The more complex spectra for these compounds reveal the hindrance of the rotation of the nonsymmetric ring B at room temperature. The room-temperature ^{1}H NMR spectrum of **9** (Figure 5) exhibits two doublets for the axial protons (δ = 3.11 and 3.16 ppm) and two doublets of doublets for the equatorial protons (δ = 3.27 and 3.33 ppm; the further splitting of the signals is due to the long-range coupling characteristics of the equatorial protons of the 1,3-dioxane ring[19] of the dioxacyclohexane rings and the signals pertaining to the protons of the different CH_2 groups are AB systems (Table 2, Figure 5). The structure of cyclophane **9** belongs to the C_s symmetry point group and exhibits planar prochirality. Positions 2′(2′′) and 4′(4′′) (CH_2 groups of the same dioxacyclohexane ring) are diastereotopic, as well as the protons of the same CH_2 group (either at positions 2 and 13 or at positions 4 and 11).[20] The two dioxacyclohexane rings (C and D), the two benzyl-type CH_2 groups (2 and 13), and the CH_2 groups at positions 4 and 11 are not different in the NMR spectrum. An interesting feature in the ^{1}H NMR spectrum of **9** is the recording of different signals (δ = 6.06 and 7.03 ppm) for the protons of the 1,4-phenylene ring. This fact proves the hindrance of the rotation of the 1,4-phenylene ring, too. Thus, in compound **9**, the room-temperature rotation of both aromatic rings A and B is blocked. In order to observe the rotation of the rings, variable-temperature ^{1}H NMR experiments (in [D$_6$]DMSO) were carried out with **9** by raising the temperature to 390 K (a limit imposed by the apparatus). The spectra at high temperatures did not show significant modifications compared with the spectra run at room temperature, but they proved the hindrance of the rotation of the aromatic rings even at these temperatures. We estimated (using Eyring's equations)[21] the barrier for the rotation of the aromatic rings in **9** to be higher than 20.1 kcal/mol.

Molecular modeling predicts for **11** and **12** more stable *syn* structures (Figure 6; $\Delta G^{\circ}_{anti\text{–}syn}$ = 1.19 and 1.95 kcal/mol, respectively) and lower barriers for the flipping of the bridges [$\Delta G^{\#}$(**11**) = 15.12 and $\Delta G^{\#}$(**12**) = 14.04 kcal/mol] than for the rotation of the aromatic rings. The rotation of ring B can occur in two ways: either with the nitrogen atom or the CH group inside the cyclophane. For **12** only the rotation with the CH group inside is thermodynamically possible [$\Delta G^{\#}$(**12**) = 23.85 kcal/mol], while for **11** both routes can be followed, but the calculated barrier for the rotation with the nitrogen atom inside is lower [$\Delta G^{\#}$(**11**) = 15.08 and 22.31 kcal/mol for the rotation with the nitrogen atom or the CH group inside, respectively].



11 ***syn***



11 ***anti***

Figure 6. *syn* and *anti* isomers of **11** (the distances between the nitrogen atom and the centroid of A are 3.767 and 4.239 Å, respectively).

The room-temperature NMR spectra of these compounds show only one set of signals, with differentiation of the CH$_2$ groups of the same dioxacyclohexane ring and of the protons of the same CH$_2$ group of the bridges, and suggest (at room temperature) the fast flipping of the chains and hindrance of the rotation of the pyridine and pyridine oxide groups. The ^{1}H NMR spectra of **11** and **12** (Figures 7, 8, and 9) are more complex than the spectrum of **9**. Compounds **11** and **12** belong to the C_1 symmetry point group. The plane of symmetry found in **9** does not exist in **11** and **12**. As a consequence, the two dioxacyclohexane rings (C and D), the two benzyl-type methylene groups (positions 2 and 13), and the other two methylene groups (positions 4 and 11) are different in the NMR spectra. At the same time, if the rotation of the pyridine ring is frozen, the planar chi-

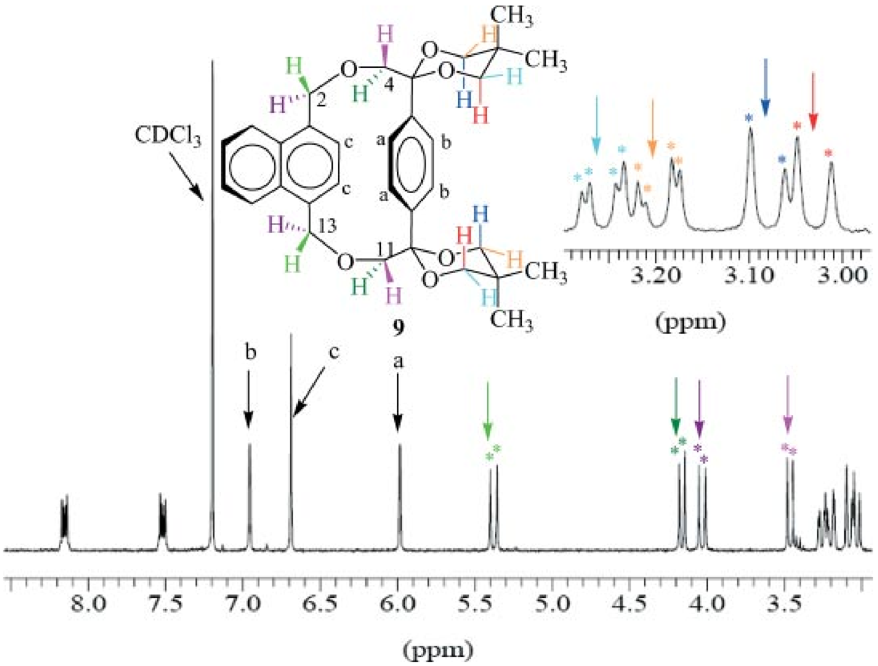


Figure 5. ^{1}H NMR spectrum (room temp., CDCl$_3$, 300 MHz, fragment) of **9**.

rality of **11** and **12** determines the diastereotopicity of the similar groups of the same dioxacyclohexane ring (ring C: positions 2′ and 4′; ring D: positions 2′′ and 4′′) and of the protons of the same CH_2 group. The room-temperature ^1H NMR spectrum of **11** ([D$_8$]THF, 500 MHz, Figure 7c) exhibits three different signals (two doublets at δ = 6.83 and 6.96 ppm and a singlet at δ = 7.11 ppm) for the protons of the 1,4-phenylene group and reveals a parallel orientation of the aromatic rings and hindrance to their rotation. The protons of the four methylene groups (positions 2, 4, 11, and 13) display eight doublets in the range from δ = 3.36 to 4.42 ppm, while the signals (eight doublets) corresponding to the axial and equatorial protons of the dioxacyclohexane rings (C and D) overlap and give a complex pattern (δ = 3.19–3.36 ppm). The spectrum of **11** at 300 K in [D$_6$]DMSO (400 MHz, Figure 8a) exhibits a similar pattern to that recorded in [D$_8$]THF. These NMR spectra (recorded at room temperature) suggest the freezing of the rotation of the aromatic rings and the flipping of the chains (the spectra do not exhibit separated signals for the *syn* and *anti* structures). In order to obtain more details about the conformational behavior of **11**, variable-temperature NMR experiments were carried out, either by increasing the temperature in [D$_6$]DMSO (Figure 8) or by lowering the temperature in [D$_8$]THF (Figure 7). The spectrum at 340 K ([D$_6$]DMSO, 400 MHz, Figure 8b) shows coalescence, while the spectrum recorded at 400 K (Figure 8c) reveals the rapid rotation of the pyridine ring at this temperature. The protons of the 1,4-phenylene group denoted as 7, 8, 17 and 18, as well as the protons of the same methylene groups or the axial and equatorial protons of the different positions of the dioxacyclohexane rings C and D (positions 2′ and 4′ or 2′′ and 4′′) are rendered equivalent by the dynamics of the cyclophane, and the spectrum at 400 K (Figure 8c) is considerably more simple than that at room-temperature. The protons of the 1,4-phenylene group exhibit an AA′BB′ system, the axial and equatorial protons of the two dioxacyclohexane rings exhibit two doublets (δ = 3.22 and

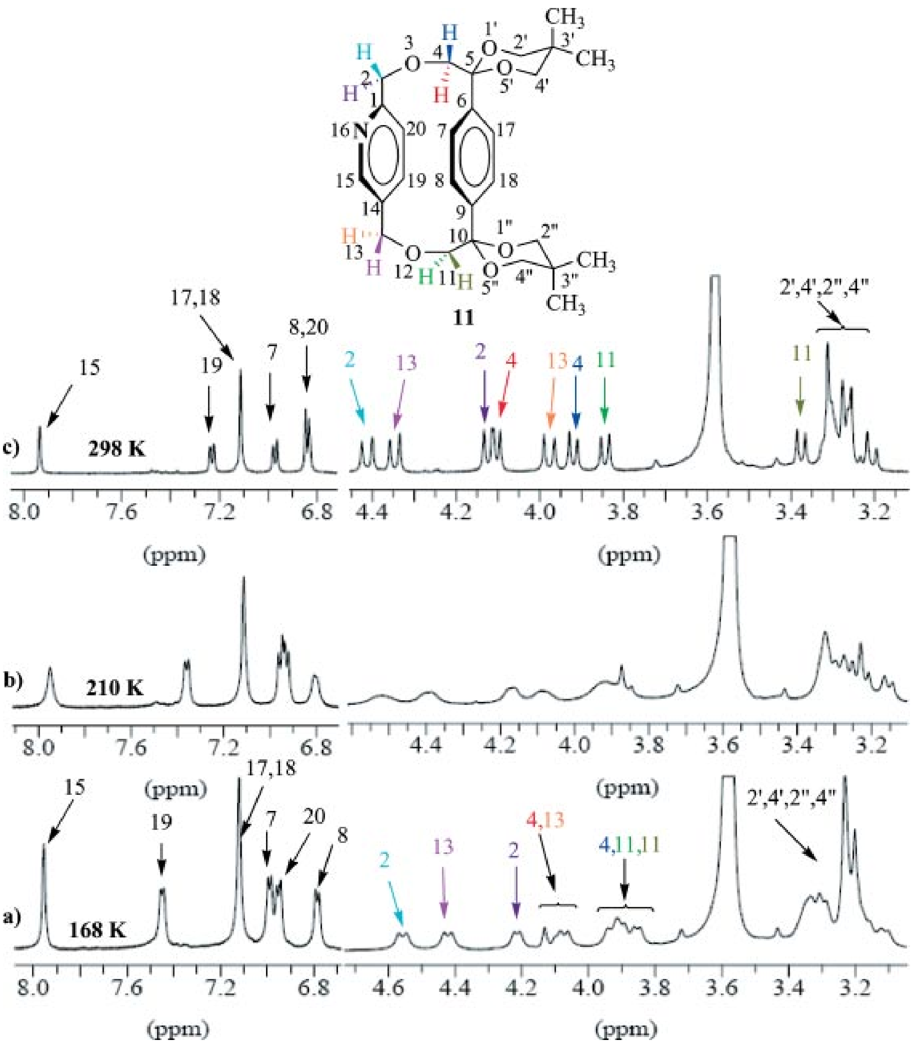


Figure 7. ^1H NMR spectra (500 MHz) of compound **11** in [D$_8$]THF at 168 (a), 210 (b), and 298 K (c).

3.38 ppm; differences between the dioxacyclohexane rings C and D are not observed), while the protons of the four CH_2 groups of the chains display four singlets (δ = 3.69, 3.94, 4.25, and 4.27 ppm; the protons of the same CH_2 group are rendered equivalent by the rotation of the pyridine ring). A barrier of $\Delta G^{\#}$ = 16.44 ± 0.18 kcal/mol was calculated (using Eyring's equations)[21] for the rotation of the aromatic rings in **11**. The variable-temperature NMR experiment carried out in [D$_8$]THF by decreasing the temperature led to the observation of the coalescence of different signals (e.g., at 210 K, Figure 7b). The spectrum at 168 K shows clear signals and suggests the freezing of the flipping of the chains. Unfortunately, the differences in the magnetic environments of similar protons in the frozen *syn* and *anti* structures are insignificant, and in the low-temperature spectrum (168 K) the signals belonging to the *syn* and *anti* isomers are not separated. The ratio of the two isomers and the barrier for the flipping of the chains could not be calculated from these experiments. However, the modifications to the spectra caused by lowering the temperature (individual signals at room temperature, coalescence at 210 K, and again individual signals at 168 K) shows clearly the freezing of the second conformational equilibrium which corresponds to the flipping of the bridges.

The room-temperature ^{1}H NMR spectrum (CD_2Cl_2, Figure 9) of the *N*-oxide **12** is similar to the room-temperature spectrum of **11**, but the better differentiation of the signals pertaining to rings C and D was noticed. The variable-temperature NMR experiments carried out on this compound by increasing the temperature showed that coalescence of the signals did not occur below 400 K, so the rotation of the pyridine *N*-oxide ring is still hindered at this temperature. The barrier ($\Delta G^{\#}$) for the rotation of the aromatic rings was estimated to be higher than 20.1 kcal/mol. More important results were obtained by decreasing the temperature; at 230 K Figure 9c), coalescence processes could be observed. At 180 K the spectrum (Figure 9d) exhibits two sets of signals belonging to the *syn* (major) and *anti* isomers. The ratio between the *syn* and *anti* isomers calculated from the low-temperature NMR spectrum is 1.60:1.00, which is in good agreement with the value (*syn*/*anti* = 1.69:1.00) obtained by molecular modeling. By using the data obtained from the variable-temperature NMR spectra and Eyring's equations,[21] we calculated the barrier ($\Delta G^{\#}$ = 10.4 ± 0.5 kcal/mol) for the flipping of the bridges (Scheme 4), the experimental value being somewhat smaller than the one calculated by molecular modeling ($\Delta G^{\#}$ = 14.04 kcal/mol).

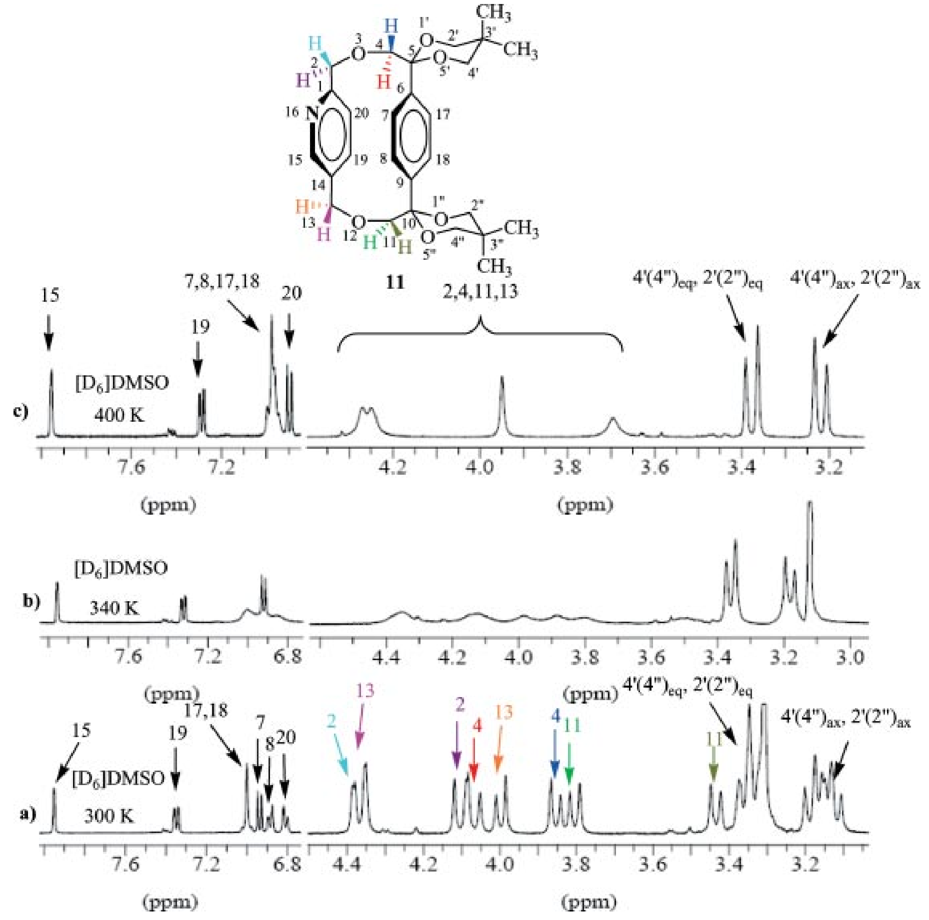


Figure 8. ^{1}H NMR spectra (400 MHz) of compound **11** in [D$_6$]DMSO at 300 (a), 340 (b), and 400 K (c).

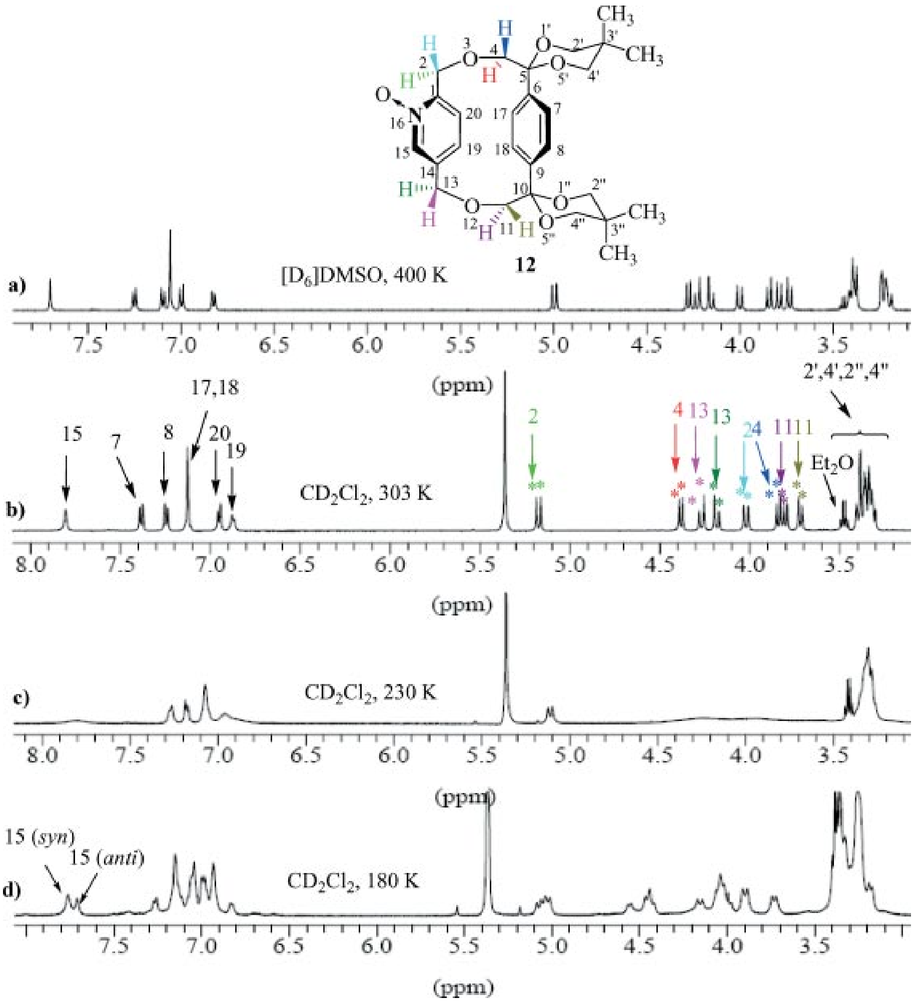


Figure 9. ^{1}H NMR spectra (fragments, 500 MHz) of compound **12** in [D$_6$]DMSO at 400 K (a) and in CD$_2$Cl$_2$ at 303 (b), 230 (c), and 180 K (d).

The ^{1}H NMR spectra of compound **14** reveal the hindrance of the rotation of the aromatic groups. Positions 2′ and 4′ (Table 2) of the saturated heterocycle give different signals (δ_{ax} = 3.17 and 3.21 ppm; δ_{eq} = 3.31 and 3.35 ppm), so they are diastereotopic. The protons of the same CH$_2$ group are diastereotopic as well as the protons of the four CH$_2$ groups of the chains which exhibit eight doublets (as in the case of **11** and **12**). The difficulties encountered in the hydrolysis of the 1,3-dioxane rings are due to the contraction of the cyclophane when carbonyl groups are generated (sp^3 carbon atoms are replaced by sp^2 carbon atoms). The new geometries induced by the sp^2 carbon atoms bring closer the aromatic units of the cyclophanes (molecular modeling results are shown in the Supporting Information). It is worth comparing the distances between the *ortho*,*ortho′* hydrogen atoms of ring B and the center of ring A in the edge-tilted-to-face structures of **7** and **15** which are 3.078 and 2.617 Å, respectively, and also to compare the chemical shifts of the pertinent protons of **7**, **13**, and **15**. The ^{1}H NMR spectra of these compounds (Figure 10) reveal a shielding of the *ortho*,*ortho′* protons in **7** (δ = 6.28 ppm), a greater shielding of more than 0.5 ppm in the monoketone **13** (δ = 5.62 ppm), and a quite incredible position of this signal (δ = 4.96 ppm) in the spectrum of diketone **15**. The shielding of the signal for this proton is important and comparable with spectacular cases presented in the literature.[3a,22]

Conclusions

X-ray diffraction, NMR spectroscopy, and molecular-modeling-based structural analysis of the new [4.4]cyclophanes **6**–**9** and **11**–**16** have revealed important C–H–π (for **6**, **7**, **13**, and **15**) and π–π (for **9** and **14**) stacking interactions either in the solid state or in solution. The rotation of the aromatic groups and the flipping of the bridges for some of these compounds were monitored step-by-step by variable-temperature NMR experiments. The higher barrier for the rotation of the aromatic rings than for the flipping of the bridges and the preference of **7**, **11**, and **12** for *syn* structures were revealed. The good correlation between the calculated (using molecular modeling data) and experimental (based on low-temperature NMR spectra) ratios of the

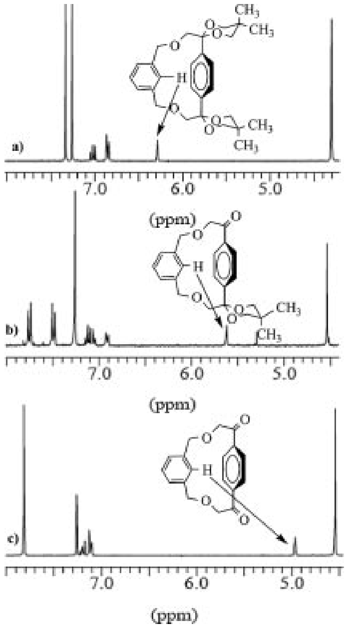


Figure 10. ^{1}H NMR spectra ($CDCl_3$, 300 MHz) at room temp. of compounds **7** (a), **13** (b), and **15** (c).

syn and *anti* isomers of **12** was noticed. Dioxo[4.4]cyclophanes **15** and **16** could be obtained in good overall yields starting from simple compounds and by using an original strategy (with CAN and HCl) for the deprotection of the cyclic ketals.

Experimental Section

General Experimental Data: Chemicals were purchased from Aldrich or Acros and were used without further purification. Unless otherwise stated, routine ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra, COSY, HMQC, and HMBC were recorded at room temp. in $CDCl_3$ with a Bruker 300 MHz spectrometer using the solvent line as reference. Variable-temperature NMR and NOESY spectra were recorded with a Bruker 400, 500, or 600 MHz spectrometer, respectively, in $CDCl_3$, CD_2Cl_2, [D$_8$]THF, or [D$_6$]DMSO. The FID was retreated by applying a Gaussian curve (GB 0.2 and LB-5) in the cases of **11**–**13**. Melting points were measured with a Kleinfeld melting-point apparatus and are uncorrected. Microanalyses (C, H, N) agreed (within ±0.4%) with calculated data. Mass spectra were recorded with an ATI Unicam Automass fitted spectrometer. Thin-layer chromatography (TLC) was conducted on silica gel 60 F_{254} TLC plates purchased from Merck. Preparative column (flash) chromatography was preformed using PharmPrep 60 CC (40–63 µm) silica gel purchased from Merck. The calculations were carried out by using the Spartan04 (Spartan'04 Wavefunction, Inc., Irvine, CA) suite of programs. Energy profiles for the rotation of ring B against ring A were constructed at the PM3 level of theory by constraining the specific dihedrals (which define the motion of the ring) and fully optimizing the rest of coordinates.[23] Bridge flipping was similarly treated by restraining the rotations around the bridging O–CH_2 single bonds and by fully optimizing the remaining coordinates. In order to check the validity of the PM3 results, the B3LYP hybrid density functional with the 6-31G(d) basis set[24] was used to search for the transition state for rotation of ring B in **7** and **8**. The nature of the stationary points was checked by frequency analysis (at the same level of theory), which showed that both transition states (**TS 7B** and **TS 8B**; discussed in the Supporting Information) are genuine ones (i.e., they have only one imaginary frequency and the corresponding normal modes are related to the rotation of ring B). B3LYP/6-31G(d) geometry optimizations of **6**, **7** (*anti*, *syn*), **8**, **11** (*anti*, *syn*), **12** (*anti*, *syn*), **13** (*anti*, *syn*), and **15** (*anti*, *syn*) were carried out and the corresponding equilibrium geometries are shown in the Supporting Information. However, due to the size of these systems, no further frequency calculations were undertaken. CCDC-241320 (for **6**), -273535 (for **7**), -255757 (for **9**), and -278082 (for **15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Synthesis of [4.4]Cyclophanes 6–9 and 11: Diol **5** (250 mg, 0.68 mmol) in dry THF (10 mL) was added, under argon, to a suspension of NaH (65 mg, 2.72 mmol) in dry THF (400 mL). The mixture was refluxed and dibrominated compounds **1**–**4** or **10** (0.68 mmol) dissolved in THF (80 mL) were added to the solution over 4 d, under reflux, using a sensitive push-syringe. Refluxing of the solvent was continued for an additional 1 d, after which the system was cooled to room temp. and the solid phase removed by filtration. The solvent was evaporated, and the crude product was dissolved in CH_2Cl_2 (20 mL) and then washed twice with water (20 mL). After drying with $MgSO_4$, the solvent was removed and the crude product was purified by flash chromatography.

5,5,10,10-Bis(3′,3′-dimethyl-1′,5′-dioxapentane-1′,5′-diyl)-3,12-dioxatricyclo[12.4.2^{6,9}.0^{1,14}]icosa-1(18),6,8,14,16,19-hexaene (6): White crystals, yield 34% (107 mg, 0.28 mmol), m.p. 210–211 °C. Purified by flash chromatography (silica gel, diethyl ether/pentane = 2:3), $R_f = 0.44$. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.67$ (s, 6 H, 3′-CH_{3eq}), 1.30 (s, 6 H, 3′-CH_{3ax}), 3.46 (s, 4 H, 4-H, 11-H), 3.51 (d, $^2J = 10.9$ Hz, 4 H, 2′-H_{ax}, 4′-H_{ax}), 3.53 (s, 4 H, 2-H, 13-H), 3.72 (d, $^2J = 10.9$ Hz, 4 H, 2′-H_{eq}, 4′-H_{eq}), 7.15 (m, 2 H, 16-H, 17-H), 7.29 (m, 2 H, 15-H, 18-H), 7.41 (s, 4 H, 7-H, 8-H, 19-H, 20-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.0$ (3′-CH_{3eq}), 23.0 (3′-CH_{3ax}), 30.8 (C-3′), 70.5 (C-4, C-11), 71.9 (C-2′, C-4′), 78.4 (C-2, C-13), 101.2 (C-5, C-10), 127.4 (C-15, C-18), 128.3 (C-16, C-17), 129.0 (C-7, C-8, C-19, C-20), 135.0 (C-6, C-9), 137.6 (C-1, C-14) ppm. MS (EI, 70 eV): *m*/*z* (%) = 468 (2) [M]$^+$, 438 (30), 317 (10), 204 (42), 104 (100), 69 (96). $C_{28}H_{36}O_6$ (468.58): calcd. C 71.77, H 7.74; found C 71.89, H 7.68.

5,5,10,10-Bis(3′,3′-dimethyl-1′,5′-dioxapentane-1′,5′-diyl)-3,12-dioxatricyclo[12.3.2^{6,9}.1^{1,14}]icosa-1(20),6,8,14,16,18-hexaene (7): White crystals, yield 49% (156 mg, 0.33 mmol), m.p. 217–218 °C. Purified by flash chromatography (silica gel, diethyl ether/pentane = 2:3), $R_f = 0.62$. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.65$ (s, 6 H, 3′-CH_{3eq}), 1.29 (s, 6 H, 3′-CH_{3ax}), 3.47 (d, $^2J = 10.6$ Hz, 4 H, 2′-H_{ax}, 4′-H_{ax}), 3.57 (s, 4 H, 4-H, 11-H), 3.63 (d, $^2J = 10.6$ Hz, 4 H, 2′-H_{eq}, 4′-H_{eq}), 4.30 (s, 4 H, 2-H, 13-H), 6.28 (s, 1 H, 20-H), 6.85 (d, $^3J = 7.5$ Hz, 2 H, 15-H, 17-H), 6.99 (t, $^3J = 7.5$ Hz 1 H, 16-H), 7.33 (s, 4 H, 7-H, 8-H, 18-H, 19-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.1$ (3′-CH_{3eq}) 23.0 (3′-CH_{3ax}), 30.7 (C-3′), 71.7 (C-2′, C-4′), 72.6 (C-2, C-13), 77.2 (C-4, C-11), 100.6 (C-5, C-10), 126.9 (C-16), 127.3 (C-15, C-17), 128.0 (C-7, C-8, C-18, C-19), 128.4 (C-20), 137.3 (C-6, C-9), 137.9 (C-1, C-14) ppm. MS (EI, 70 eV): *m*/*z* (%) = 468 (0.4) [M]$^+$, 438 (69), 408 (7), 190 (19), 149 (9), 104 (100), 69 (62). $C_{28}H_{36}O_6$ (468.58): calcd. C 71.77, H 7.74; found C 71.81, H 7.66.

5,5,10,10-Bis(3′,3′-dimethyl-1′,5′-dioxapentane-1′,5′-diyl)-3,12-dioxatricyclo[12.2.2^{6,9}.2^{1,14}]icosa-1(20),6,8,14(19),15,17-hexaene (8):

White crystals, yield 67% (215 mg, 0.46 mmol), m.p. 219–220 °C. Purified by flash chromatography (silica gel, diethyl ether/pentane = 1:1), R_f = 0.37. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.55 (s, 6 H, 3′-CH$_{3eq}$), 1.23 (s, 6 H, 3′-CH$_{3ax}$), 3.31 (d, ^{2}J = 10.6 Hz, 4 H, 2′-H$_{ax}$, 4′-H$_{ax}$), 3.37 (d, ^{2}J = 10.6 Hz, 4 H, 2′-H$_{eq}$, 4′-H$_{eq}$), 3.78 (s, 4 H, 4-H, 11-H), 4.27 (s, 4 H, 2-H, 13-H), 6.87 (s, 4 H, 7-H, 8-H, 17-H, 18-H), 7.02 (s, 4 H, 15-H, 16-H, 19-H, 20-H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.1 (3′-CH$_{3eq}$) 22.9 (3′-CH$_{3ax}$), 30.5 (C-3′), 71.3 (C-2′, C-4′), 73.4 (C-2, C-13), 76.0 (C-4, C-11), 99.5 (C-5, C-10), 127.7 (C-15, C-16, C-19, C-20), 129.7 (C-7, C-8, C-17, C-18), 136.5 (C-6, C-9), 136.6 (C-1, C-14) ppm. MS (EI, 70 eV): *m*/*z* (%) = 469 (2) [M]$^+$, 438 (59), 190 (30), 149 (15), 104 (100), 69 (96). $C_{28}H_{36}O_6$ (468.58): calcd. C 71.77, H 7.74; found C 71.77, H 7.67.

5,5,10,10-Bis(3′,3′-dimethyl-1′,5′-dioxapentane-1′,5′-diyl)-3,12-dioxatetracyclo[12.6.2^{6,9}.2^{1,14}.0^{15,20}]tetracosa-1(24),6,8,14(23),15,17,19,21-octaene (9): White crystals, yield 52% (183 mg, 0.35 mmol), m.p. 238–239 °C. Purified by flash chromatography (silica gel, diethyl ether/pentane = 1:2), R_f = 0.31. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.46 (s, 6 H, 3′-CH$_{3eq}$), 1.20 (s, 6 H, 3′-CH$_{3ax}$), 3.09 (d, ^{2}J = 10.9 Hz, 2 H, 2′-H$_{ax}$), 3.14 (d, ^{2}J = 10.9 Hz, 2 H, 4′-H$_{ax}$), 3.26 (dd, ^{2}J = 10.9, ^{4}J = 2.6 Hz, 2 H, 4′-H$_{eq}$), 3.32 (dd, ^{2}J = 10.9, ^{4}J = 2.6 Hz, 2 H, 2′-H$_{eq}$), 3.52 (d, ^{2}J = 10.0 Hz, 2 H, 4-C*H*H, 11-C*H*H), 4.09 (d, ^{2}J = 12.8 Hz, 2 H, 2-C*H*H, 13-C*H*H), 4.22 (d, ^{2}J = 10.0 Hz, 2 H, 4-CH*H*, 11-CH*H*), 5.44 (d, ^{2}J = 12.8 Hz, 2 H, 2-CH*H*, 13-CH*H*), 6.05 (d, ^{4}J = 1.1 Hz, 2 H, 7-H, 8-H), 6.75 (s, 2 H, 23-H, 24-H), 7.02 (d, ^{4}J = 1.1 Hz, 2 H, 21-H, 22-H), 7.58 (m, 2 H, 17-H, 18-H), 8.21 (m, 2 H, 16-H, 19-H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.0 (3′-CH$_{3eq}$), 22.9 (3′-CH$_{3ax}$), 30.4 (C-3′), 71.2 (C-2′, C-4′), 72.2 (C-2, C-13), 76.0 (C-4, C-11), 99.3 (C-5, C-10), 125.5 (C-16, C-19), 125.8 (C-23, C-24), 126.0 (C-17, C-18), 126.8 (C-21, C-22), 127.2 (C-7, C-8), 133.0 (C-15, C-20), 134.3 (C-1, C-14), 136.4 (C-6, C-9) ppm. MS (EI, 70 eV): *m*/*z* (%) = 518 (3.6) [M]$^+$, 488 (100), 190 (41), 154 (21), 104 (63), 69 (89). $C_{32}H_{38}O_6$ (518.64): calcd. C 74.11, H 7.39; found C 74.29, H 7.20.

5,5,10,10-Bis(3′,3′-dimethyl-1′,5′-dioxapentane-1′,5′-diyl)-3,12-dioxa-16-azatricyclo[12.2.2^{6,9}.2^{1,14}]icosa-1(20),6(17),7,9,14(19),15-hexaene (11): White crystals, yield 43% (138 mg, 0.29 mmol), m.p. 164–165 °C. Purified by flash chromatography (silica gel, dichloromethane/methanol = 4:0.1), R_f = 0.25. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.560 [s, 3 H, 3′(3′′)-CH$_{3eq}$]*, 0.564 [s, 3 H, 3′(3′′)-CH$_{3eq}$],* 1.23 (s, 6 H, 3′-CH$_{3ax}$, 3′′-CH$_{3ax}$), 3.33–3.43 (overlapped signals, 8 H, 2′-H$_{ax}$, 4′-H$_{ax}$, 2′′-H$_{ax}$, 4′′-H$_{ax}$, 2′-H$_{eq}$, 4′-H$_{eq}$, 2′′-H$_{eq}$, 4′′-H$_{eq}$), 3.49 (d, ^{2}J = 9.6 Hz, 1 H, 11-C*H*H), 3.89 (d, ^{2}J = 9.6 Hz, 1 H, 11-CH*H*), 4.02 (d, ^{2}J = 9.6 Hz, 1 H, 4-C*H*H), 4.10 (d, ^{2}J = 12.5 Hz, 1 H, 13-C*H*H), 4.11 (d, ^{2}J = 9.6 Hz, 4-CH*H*), 4.27 (d, ^{2}J = 12.0 Hz, 1 H, 2-C*H*H), 4.49 (d, ^{2}J = 12.5 Hz, 1 H, 13-CH*H*), 4.50 (d, ^{2}J = 12.0 Hz, 1 H, 2-CH*H*), 6.90 (d, ^{3}J = 7.5 Hz, 1 H, 20-H), 6.92 (d, ^{3}J = 8.0 Hz, 1 H, 8-H), 7.03 (d, ^{3}J = 8.0 Hz, 1 H, 7-H), 7.19 (s, 2 H, 17-H, 18-H), 7.21 (dd, ^{3}J = 7.5, ^{4}J = 2.6 Hz, 1 H, 19-H), 8.04 (d, ^{4}J = 2.6 Hz, 1 H, 15-H) ppm; *unassigned signals. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.08 [3′(3′′)-CH$_{3eq}$]*, 22.12 [3′(3′′)-CH$_{3eq}$]*, 22.95 [3′(3′′)-CH$_{3ax}$]*, 22.99 [3′(3′′)-CH$_{3ax}$]*, 30.5 (C-3′, C-3′′), 70.8 (C-13), 71.2, 71.3, 71.4 (C-2′, C-4′, C-2′′, C-4′′),* 73.8 (C-2), 75.9 (C-11), 76.4 (C-4), 99.4 (C-10), 99.5 (C-5), 123.0 (C-20), 126.6 (C-8), 127.4 (C-17), 128.4 (C-18), 128.6 (C-7), 130.9 (C-14), 136.3 (C-9), 137.04 (C-6), 137.08 (C-19), 150.9 (C-15), 156.3 (C-1) ppm; *unassigned signals. MS (EI, 70 eV): *m*/*z* (%) = 469 (3) [M]$^+$, 439 (89), 303 (9), 190 (19), 104 (84), 69 (100). $C_{27}H_{35}NO_6$ (469.57): calcd. C 69.06, H 7.51, N 2.98; found C 68.88, H 7.70, N 3.07.

Procedure for the Synthesis of Compound 12: *m*-Chloroperoxybenzoic acid (70%, 41.89 mg, 0.17 mmol) was added portionwise to a solution of **11** (80 mg, 0.17 mmol) in dichloromethane (5 mL) at 0 °C and the mixture was stirred at this temperature for 45 min. Then the reaction mixture was successively washed with saturated NaHCO$_3$ (3 × 10 mL) and brine (10 mL). After drying with MgSO$_4$, the solvent was removed and the crude product was purified by flash chromatography.

16-Oxo-5,5,10,10-bis(3′,3′-dimethyl-1′,5′-dioxapentane-1′,5′-diyl)-3,12-dioxa-16-azatricyclo[12.2.2^{6,9}.2^{1,14}]icosa-1(20),6(17),7,9(19),14,15-hexaene (12): White crystals, yield 83% (68 mg, 0.14 mmol), m.p. 235–236 °C. Purified by flash chromatography (silica gel, dichloromethane/methanol = 2:0.1), R_f = 0.4. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.560 (s, 6 H, 3′-CH$_{3eq}$, 3′′-CH$_{3eq}$), 1.20 (s, 6 H, 3′-CH$_{3ax}$, 3′′-CH$_{3ax}$), 3.23–3.39 (overlapped signals, 8 H, 2′-H$_{ax}$, 4′-H$_{ax}$, 2′′-H$_{ax}$, 4′′-H$_{ax}$, 2′-H$_{eq}$, 4′-H$_{eq}$, 2′′-H$_{eq}$, 4′′-H$_{eq}$), 3.65 (d, ^{2}J = 9.8 Hz 1 H, 11-C*H*H), 3.87 (d, ^{2}J = 9.8 Hz 1 H, 11-CH*H*), 4.02 (d, ^{2}J = 10.2 Hz, 1 H, 4-C*H*H), 4.10 (d, ^{2}J = 12.8 Hz, 1 H, 2-C*H*H), 4.13 (d, ^{2}J = 12.5 Hz, 13-CH*H*), 4.28 (d, ^{2}J = 12.5 Hz, 1 H, 13-C*H*H), 4.49 (d, ^{2}J = 10.2, 1 H, 4-CH*H*), 5.25 (d, ^{2}J = 12.8, 1 H, 2-CH*H*), 6.77 (dd, ^{3}J = 7.9, ^{4}J = 1.5 Hz, 1 H, 19-H), 6.91 (d, ^{3}J = 7.9 Hz, 1 H, 20-H), 7.07 (dd, ^{3}J = 8.2, ^{4}J = 1.9 Hz, 1 H, 18-H), 7.15 (dd, ^{3}J = 8.2, ^{4}J = 1.9 Hz, 1 H, 17-H), 7.26 (dd, ^{3}J = 7.9, ^{4}J = 1.9 Hz, 1 H, 8-H), 7.45 (dd, ^{3}J = 7.9, ^{4}J = 1.9 Hz, 1 H, 7-H), 7.70 (d, ^{4}J = 1.5 Hz, 1 H, 15-H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.08 [3′(3′′)-CH$_{3eq}$]*, 22.18 [3′(3′′)-CH$_{3eq}$]*, 22.89 [3′(3′′)-CH$_{3ax}$]*, 22.92 [3′(3′′)-CH$_{3ax}$]*, 30.4 (C-3′, C-3′′), 65.8 (C-2), 70.3 (C-13), 71.2, 71.39, 71.44, 71.48 (C-2′, C-4′, C-2′′, C-4′′)*, 77.3 (C-11), 79.1 (C-4), 99.2 (C-10), 99.6 (C-5), 126.0 (C-19), 126.7 (C-18), 127.2 (C-20), 127.5 (C-7), 128.4 (C-8), 128.9 (C-17), 135.1 (C-9), 136.5 (C-6), 137.4 (C-14), 140.6 (C-15), 147.4 (C-1) ppm; *unassigned signals. MS (EI, 70 eV): *m*/*z* (%) = 485 (1.1) [M]$^+$, 440 (44), 233 (11), 190 (24), 149 (16), 104 (68), 69 (100). $C_{27}H_{35}NO_7$ (485.57): calcd. C 66.79, H 7.27, N 2.88; found C 66.92, H 7.43, N 2.71.

General Procedure for the Synthesis of [4.4]Cyclophanes 13 and 14: Solid cerium ammonium nitrate (CAN, 12 mg, 10 mol-%) was added to a stirred solution of compound **7** or **9** (0. 214 mmol) in MeCN (3 mL) and water (3 mL). The solution was refluxed for 12 h. After cooling to room temperature, water (5 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The organic layers were dried with MgSO$_4$, filtered, and the solvent was evaporated in vacuo. The crude product was further purified by flash chromatography.

5-Oxo-10,10-(3′,3′-dimethyl-1′,5′-dioxapentane-1′,5′-diyl)-3,12-dioxatricyclo[12.3.2^{6,9}.1^{1,14}]icosa-1(20),6,8,14,16,18-hexaene (13): White crystals, yield 74% (60 mg, 0.15 mmol), m.p. 184–185 °C. Purified by flash chromatography (silica gel, diethyl ether/pentane = 2:3), R_f = 0.60. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.63 (s, 3 H, 3′-CH$_{3eq}$), 1.29 (s, 3 H, 3′-CH$_{3ax}$), 3.49 (d, ^{2}J = 11.2 Hz, 2 H, 2′-H$_{ax}$, 4′-H$_{ax}$), 3.56 (s, 2 H, 11-H), 3.59 (d, ^{2}J = 11.2 Hz, 2 H, 2′-H$_{eq}$, 4′-H$_{eq}$), 4.11 (s, 2 H, 13-H), 4.34 (s, 2 H, 2-H), 5.53 (s, 2 H, 4-H), 5.62 [t, (dd overlapped), 1 H, 20-H], 6.91 (dt, ^{3}J = 7.2, ^{4}J = 1.5 Hz, 1 H, 15-H), 7.05 (dt, ^{3}J = 7.5, ^{4}J = 1.5 Hz, 1 H, 17-H), 7.12 [t, (dd overlapped), 1 H, 16-H), 7.49 (d, ^{3}J = 8.3 Hz, 2 H, 8-H, 18-H), 7.74 (d, ^{3}J = 8.3 Hz, 2 H, 7-H, 19-H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.0 (3′-CH$_{3eq}$), 23.0 (3′-CH$_{3ax}$), 30.7 (C-3′), 71.9 (C-2′, C-4′), 72.6 (C-2), 73.1 (C-13), 75.8 (C-4), 76.7 (C-11), 100.5 (C-10), 127.3 (C-16), 127.8 (C-15, C-17), 128.0 (C-20), 128.5 (C-8, C-18), 129.1 (C-7, C-19), 136.2 (C-1), 136.8 (C-14), 138.3 (C-6), 142.6 (C-9), 205.7 (C-5) ppm. MS (FAB$^+$): *m*/*z* (%) = 383 (14) [M + H]$^+$. $C_{23}H_{26}O_5$ (382.45): calcd. C 72.23, H 6.85; found C 72.37, H 6.73.

5-Oxo-10,10-(3′,3′-dimethyl-1′,5′-dioxapentane-1′,5′-diyl)-3,12-dioxatetracyclo[12.6.2^{6,9}.2^{1,14}.0^{15,20}]tetracosa-1(24),6,8,14(23),15,

17,19,21-octaene (14): White crystals, yield 51% (42 mg, 0.1 mmol), m.p. 191–192 °C. Purified by flash chromatography (silica gel, diethyl ether/pentane = 2:3), $R_f = 0.44$. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.48 (s, 3 H, 3′-CH$_{3eq}$), 1.21 (s, 3 H, 3′-CH$_{3ax}$), 3.16 (d, ^2J = 11.3 Hz, 1 H, 2′-H$_{ax}$), 3.22 (d, ^2J = 10.9 Hz, 1 H, 4′-H$_{ax}$), 3.30 (dd, ^2J = 11.3, ^4J = 2.6 Hz, 1 H, 2′-H$_{eq}$), 3.37 (dd, ^2J = 10.9, ^4J = 2.6 Hz, 1 H, 4′-H$_{eq}$), 3.49 (d, ^2J = 10.0 Hz, 1 H, 11-C*H*H), 4.06 (d, ^2J = 13.2 Hz, 1 H, 13-C*H*H), 4.10 (d, ^2J = 10.0 Hz, 1 H, 11-CH*H*), 4.57 (d, ^2J = 15.6 Hz, 1 H, 2-C*H*H), 4.70 (d, ^2J = 13.0 Hz, 1 H, 4-C*H*H), 4.75 (d, ^2J = 15.6 Hz, 1 H, 2-CH*H*), 5.33 (d, ^2J = 13.2 Hz, 1 H, 13-CH*H*), 5.37 (d, ^2J = 13.0 Hz, 1 H, 4-CH*H*), 6.49 (dd, ^3J = 7.9, ^4J = 1.8 Hz, 1 H, 22-H), 6.52 (dd, ^3J = 7.9, ^4J = 1.8 Hz, 1 H, 21-H), 6.80 (d, ^3J = 6.8 Hz, 1 H, 23-H), 6.99 (dd, ^3J = 8.1, ^4J = 1.8 Hz, 1 H, 8-H), 7.02 (d, ^3J = 6.8 Hz, 1 H, 24-H), 7.51 (dd, ^3J = 8.1, ^4J = 1.8 Hz, 1 H, 7-H), 7.53–7.57 (m, overlapped peaks, 2 H, C-17, C-18), 8.01–8.04 (m, 2 H, C-16, C-19) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.8 (3′-CH$_{3eq}$), 22.8 (3′-CH$_{3ax}$), 30.5 (C-3′), 71.50 (C-2′), 71.56 (C-4′), 71.9 (C-13), 73.2 (C-4), 77.7 (C-2), 78.6 (C-11), 99.8 (C-10), 124.4, 125.5, 126.27, 126.29, 126.5, 126.8, 127.1, 127.8, 128.1, 128.8 (C-7, C-8, C-16, C-17, C-18, C-19, C-21, C-22, C-23, C-24),* 132.4, 132.6, 133.6, 135.2, 135.3 (C-9, C-14, C-15, C-16, C-20),* 141.6 (C-6), 200.7 (C-5) ppm; *unassigned signals. MS (EI, 70 eV): m/z (%) = 432 (10) [M]$^+$, 402 (100), 233 (49), 190 (54), 141 (50), 104 (86), 69 (62). C$_{27}$H$_{28}$O$_5$ (432.19): calcd. C 74.98, H 6.53; found C 74.77, H 6.67.

General Procedure for the Synthesis of Diketones 15 and 16: Solid cerium ammonium nitrate (CAN, 5 mg, 10 mol-%) and 6 N HCl (0.01 mL) were added to a stirred solution of compound **7** or **8** (50 mg, 0.1 mmol) in MeCN (3 mL) and water (1 mL). The solution was refluxed for 6 h. After cooling to room temperature, water (5 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The organic layers were dried with MgSO$_4$, filtered, and the solvent was evaporated in vacuo. The crude product was further purified by flash chromatography.

5,10-Dioxo-3,12-dioxatricyclo[12.3.2^{6,9}.1^{1,14}]icosa-1(20),6,8,14,16,18-hexaene (15): White crystals, yield 84% (27 mg, 0.09 mmol), m.p. 179–180 °C. Purified by flash chromatography (silica gel, diethyl ether/pentane = 2:3), $R_f = 0.43$. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.14 (s, 4 H, 2-H, 13-H), 4.54 (s, 4 H, 4-H, 11-H), 4.96 (s, 1 H, 20-H), 7.10–7.12 (overlapped peaks, 2 H, 15-H, 17-H), 7.21 (dd, ^3J = 8.3, ^3J = 8.7 Hz, 1 H, 16-H), 7.81 (s, 4 H, 7-H, 8-H, 18-H, 19-H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 73.3 (C-2, C-13), 76.0 (C-4, C-11), 128.4 (C-16), 128.5 (C-15, C-17), 129.2 (C-7, C-8, C-18, C-19), 131.3.1 (C-20), 136.7 (C-1, C-14), 139.2 (C-6, C-9), 205.2 (C-5, C-10) ppm. MS (FAB$^+$): m/z (%) = 297 (14) [M + H]$^+$. C$_{18}$H$_{16}$O$_4$ (296:32): calcd. C 72.96, H 5.54; found C 72.81, H 5.67.

5,10-Dioxo-3,12-dioxatricyclo[12.2.2^{6,9}.2^{1,14}]icosa-1(20),6,8,14(19),15,17-hexaene (16): White crystals, yield 92% (29 mg, 0.01 mmol), m.p. 172–173 °C. Purified by flash chromatography (silica gel, diethyl ether/pentane = 1:2), $R_f = 0.23$. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.49 (s, 4 H, 2-H, 13-H), 4.60 (s, 4 H, 4-H, 11-H), 6.81 (s, 4 H, 15-H, 16-H, 19-H, 20-H), 7.47 (s, 4 H, 7-H, 8-H, 17-H, 18-H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 75.9 (C-2, C-13), 77.6 (C-4, C-11), 128.7 (C-7, C-8, C-17, C-18), 129.3 (C-15, C-16, C-19, C-20), 137.8 (C-1, C-14), 138.9 (C-6, C-9), 201.4 (C-5, C-10) ppm. MS (EI, 70 eV): m/z (%) = 296 (0.5) [M]$^+$, 266 (4), 236 (26), 147 (39), 132 (53), 119 (18), 104 (100), 91 (71), 76 (62), 63 (14). C$_{18}$H$_{16}$O$_4$ (296:32): calcd. C 72.96, H 5.54; found C 72.79, H 5.58.

Supporting Information (see footnote on the first page of this article): Synthesis, procedures and characterization of the precursors, NMR determination of the barriers of rotation, X-ray determination data, results of the molecular modeling.

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