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An Experimental Study on the Effect of Substituents on Aromatic–Aromatic Interactions in Dithia[3,3]-metaparacyclophanes

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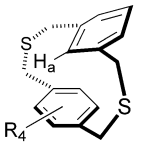
Dedicated to Professor Giuseppe Bartoli on the occasion of his 70th birthday

Abstract: Simple model systems based on the 2,11-dithia[3,3]-metaparacyclophane skeleton were synthesized to study the effects of substituents on the intramolecular aromatic–aromatic interactions between benzene rings. X-ray crystallography established that, in their more stable conformations, these metaparacyclophanes featured partially overlapping aromatic rings (interplanar distances of about 3.5 Å), with the planes of the aromatic systems arranged in a slightly tilted disposition (interplanar angles in the range 5–19°). Calculations showed that these derivatives underwent topomerization by flipping of the *meta*-substituted ring over the *para*-substituted one, a process in which the two rings adopted a continuum of edge-to-face dispositions, including an orthogonal one, which were less stable than the starting face-to-face arrangement. The energy barriers to the isomerization process were experimentally determined by variable-temperature NMR spectroscopy, by using an internal temperature standard to assess even minor differences in energy (relative experimental error: ($\pm$ 0.1 kJ mol^{-1}). The variation in the barriers as a function of the different substituents on the interacting ring was small and apparently unrelated to the effect of the substituents on the polarity of the π-systems. An explanation based on the charge-penetration effect seemed more-suitable to rationalize the observed trends in the barriers.

Keywords: aromatic–aromatic interactions · conformational analysis · substituent effects · NMR spectroscopy · X-ray diffraction

Introduction

As a part of a recent study,[1] we investigated the stereodynamic behavior of 2,11-dithia[3,3]-metaparacyclophanes **1** and **2** (Scheme 1). These molecules were selected as model systems to study the influence exerted by perfluorination of one of the rings involved in intramolecular aromatic–aromatic interactions[2] between two arenes located at a distance of about 3.5 Å from one another.



1, R = H; **2**, R = F

Scheme 1. Structures of 2,11-dithia[3,3]-metaparacyclophanes **1** and **2**.

On the basis of previous reports on related metaparacyclophanes,[3] we expected that these molecules would be conformationally flexible enough for their aromatic rings to adopt some of the typical relative dispositions that have been used to discuss the interactions between aromatic π-systems, such as the parallel-stacked- (PS), parallel-offset- (PO), and tilted- and orthogonal edge-to-face geometries (ETF; Scheme 2).[4]

DFT calculations carried out at the B3LYP/6-31G(d) level of theory[1] established that, in their ground state (GS) conformations, the aromatic systems of compounds **1** and **2** were partially overlapped and were arranged in a slightly tilted disposition with interplanar angles of about 25° and with the H_a atom of the top ring localized within the shielding cone of the platform ring. Calculations showed that, at room temperature, these derivatives readily underwent topomerization by flipping of the *meta*-substituted ring over the *para*-substituted one, a process in which the H_a atom swung over the benzene platform and the two rings adopted a continuum of EtF dispositions that featured different interplanar angles. Remarkably, at its mid-point, the topomerization

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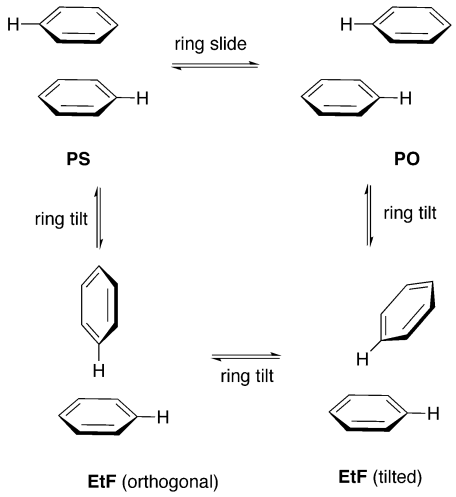


Scheme 2. Relative dispositions of two interacting benzene rings.

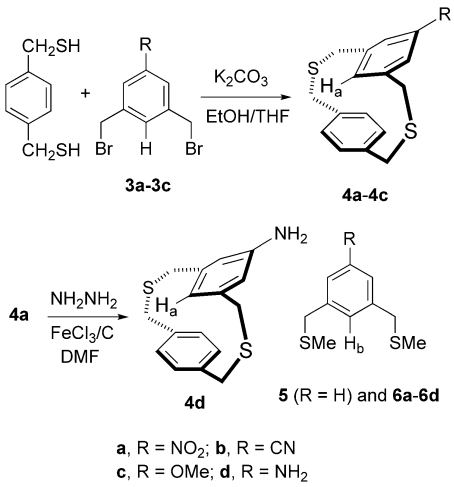
pathway for both compounds **1** and **2** showed an orthogonal EtF arrangement of the two rings, which was calculated to be a transition-state (TS) conformation that was about 15 kJ mol^{-1} less stable than the GS conformation.

Variable-temperature NMR spectroscopy (VT-NMR) confirmed the dynamic behavior predicted by these calculations and allowed us to experimentally determine the energy barriers for the topomerization. This barrier was found to be 3.0 kJ mol^{-1} higher for compound **2** than for adduct **1**.[1] This observed difference could be tentatively explained on the basis of the polar/π-rationale,[5] by considering that the GS conformation of adduct **2**, in which the π-electrons of the interacting rings were partially overlapped, was stabilized by perfluorination of the platform arene, which made their aromatic–aromatic interactions less repulsive.[5c,6] Because the TS conformations in the topomerization pathway of compounds **1** and **2** could be considered to be equally destabilized by steric effects (the threshold TS corresponded to the inversion of the relative disposition of the CH_2–S–CH_2 bridges), it would be more energetically demanding to reach the TS from the more-stable GS of adduct **2**, hence the higher barrier for this compound.[1]

On the basis of these results and as a further test of the general validity of the polar/π-rationale, we decided to undertake a more-extended, systematic study of the aromatic–aromatic interactions in a series of metaparacyclophanes, such as compounds **1** and **2**, in which the electronic distribution of the interacting rings was systematically changed by the introduction of different substituents. Herein, we report the results of this investigation.

Results and Discussion

With the aim of studying the effect of changing the electronic distribution in the top ring on the strength of the interactions, 2,11-dithia[3,3]-metaparacyclophanes **4a**–**4c** were prepared by coupling the commercially available 1,4-bis(mercaptomethyl)benzene with bis(bromomethyl) derivatives **3a**–**3c**; NH_2-substituted cyclophane **4d** was obtained by catalytic hydrogenation of its NO_2 counterpart (**4a**) in the presence of $FeCl_3$/C with hydrazine as a hydrogen source (Scheme 3). The substituents were located at the *para* position relative to the C–H_a bond to maximize electronic effects whilst minimizing the steric ones.



Scheme 3. Synthesis of 2,11-dithia[3,3]-metaparacyclophanes **4a**–**4d** and the structures of reference compounds **5** and **6a**–**6d**.

The cyclization reactions to afford compounds **4a**–**4d** were carried out in the presence of potassium carbonate under high-dilution conditions in a refluxing mixture of THF/EtOH. The desired adducts were obtained in 38–56% yield after purification by column chromatography on silica gel and crystallization. The crystal structures of these compounds (see the Experimental Section and the Supporting Information) showed the expected moderately tilted disposition of the rings, with interplanar angles of 16.5, 7.3, 18.3, and 17.0° for adducts **4a**, **4b**, **4c**, and **4d**, respectively.[7] Because these bond angles can depend on packing factors that can be particular for a given structure, even within an apparently homogeneous set of compounds, the geometries of compounds **1** and **4a**–**4d** were optimized in the gas phase by DFT calculations at the B3LYP/6-31+G(2d,p) level and at the ωB97X-D/6-311++G(2d,p) level, which included long-range correlation and dispersive effects (for details, see the Experimental Section). In both cases, the calculated structures were in fairly good agreement with the experimental data, with a limited range in the calculated interplanar angles (18.5, 20.0, 20.0, 19.1, and 21.4° at the B3LYP level and 15.5, 13.8, 13.3, 14.3, and 11.0° at the ωB97X-D level for compounds **1** and **4a**–**4d**, respectively).

The 400 MHz ^{1}H NMR data (RT, $CDCl_3$; Table 1) confirmed that the H_a atom on the top ring of compounds **4a**–**d** was located within the shielding cone of the benzene platform. Indeed, its resonance was shifted upfield relative to

Table 1. Chemical shifts of the H_a atom in compounds **1** and **4a–4d**, and of the H_b atom in compounds **5** and **6a–6d**.

Substituent	Compound	δ H_a [ppm][a]	Compound	δ H_b [ppm][b]	$\delta(H_b-H_a)$ [ppm]
NH_2	**4d**	5.03	**6d**	6.71	1.68
OMe	**4c**	5.23	**6c**	6.81	1.58
H[c]	**1**	5.60	**5**	7.24	1.64
CN	**4b**	5.85	**6b**	7.43	1.58
NO_2	**4a**	5.96	**6a**	7.41	1.45

[a] Overall variation: $\delta = 0.93$ ppm. [b] Overall variation: $\delta = 0.72$ ppm. [c] The δ H_a value for compound **1** was slightly different from that reported in reference [1] ($\delta = 5.63$ ppm) because it was re-determined under conditions identical to those employed for compounds **4a–4d**.

that of the corresponding H_b proton of (5R)-1,3-bis(methylthiomethyl)benzenes **5** and **6a–6d**, which were prepared as reference compounds to investigate the influence of a *para* substituent on the chemical shift of a proton in a related system that could not experience aromatic–aromatic interactions.

For both series of compounds (**1** and **4a–4d**, and **5** and **6a–6d**) the NMR data showed the expected downfield shift value on passing from electron-donating (amino, methoxy), to electron-neutral (hydrogen), to electron-withdrawing substituents (cyano, nitro). The presence of the platform ring slightly expanded the range of chemical-shift differences from $\delta = 0.72$ ppm for compounds **5** and **6a–6d** to $\delta = 0.93$ ppm for compounds **1** and **4a–4d**. However, a comparison across the two series showed that the difference in chemical shift, ($\delta H_b - \delta H_a$), induced by the presence of the platform ring did not correlate to the electronic character of the substituent on the top ring. For instance, the ($\delta H_b - \delta H_a$) value was the same for the NC- and MeO-substituted pairs **4b/6b** and **4c/6c** ($\delta = 1.58$ ppm), respectively. Interestingly, the NO_2-substituted compound (**4a**) showed the smallest ($\delta H_b - \delta H_a$) value ($\delta = 1.45$ ppm). Altogether, these observations suggested that a possible interaction between the $C_{Ar}-H_a$ bond of the top ring and the π-system of the bottom ring, if present and energetically significant, was not interpretable by using the polar/π-rationale.[8]

Next, we performed ^{1}H VT-NMR experiments to determine the barrier to topomerization for compounds **4a–4d**. Based on our previous work,[1] we expected the variations in energy barriers to be very small and just above the usual uncertainty involved in these measurements (0.6–1.0 kJ mol^{-1}).[9] Therefore, we decided to improve the accuracy of the barrier determination as much as possible. It is well-known that the main source of error in assessing an energy barrier by VT-NMR is the accurate determination of the temperature inside the sample. Even if a calibration curve is obtained with a thermocouple, there are other factors that make the precise determination of the temperature and its reproducibility a challenging task.[10] The best way to assess very small differences in the energy barriers would be to acquire the spectra on a mixture of two compounds, whose barriers were evaluated under identical conditions. This approach can be used provided that the two sets of exchanging signals resonate in different regions of the spectrum.[11] However, in this case, we anticipated that the signals that showed dynamic exchange (that is, those of the methylene protons of the CH_2-S-CH_2 bridges) would overlap, thus providing an extremely complex system that could not be simulated reliably. It should be also stressed that the actual temperature of the sample is not decisive, the critical factor being the exact reproducibility of the same temperature in different samples to reliably compare the rate constants obtained by the line-shape simulations.[12]

For this reason, we chose to carry out the barrier determination in the presence of a structurally different compound, which was selected as an internal "temperature-reference standard". A good candidate for this role should show a strong non-interfering signal and a very simple dynamic exchange that is extremely sensitive to small variations in temperature over a wide temperature range. We chose dimesityl ketone [bis(2,4,6-trimethylphenyl)methanone] because its strong *ortho*-methyl signal is known to show a very large broadening effect owing to the ring-flip process and to split below −169 °C with a huge chemical-shift separation (370 Hz at 600 MHz).[13] The line-width is also known to be extremely sensitive to temperature over the range −140 to −165 °C, which was expected[1] to be required for the barrier determination of adducts **4a–4d**.[14] The samples for the variable-temperature spectra were prepared by dissolving a cyclophane and dimesityl ketone in a 6:1 molar ratio in $CDFCl_2/CHF_2Cl$ (2:1 v/v).[15]

Consistent with the hypothesis of a freely occurring ring-flipping process, the 600 MHz ^{1}H VT-NMR spectra of compounds **4a–4d** showed two sharp singlets for the methylene protons of the CH_2-S-CH_2 bridges from room temperature down to −120 °C. On further lowering the temperature, the two signals broadened, and, at about −165 °C, they eventually split into four separate signals, which corresponded to two AB systems that arose from the diastereotopicity of the hydrogens within each methylene group. No other signals were observed in the spectrum, thus showing that a single conformation was significantly populated at this temperature. From the line-shape simulations of the whole spin system, we obtained the rate constants for the conformational exchange at various temperatures and derived their energy barriers (Table 2).

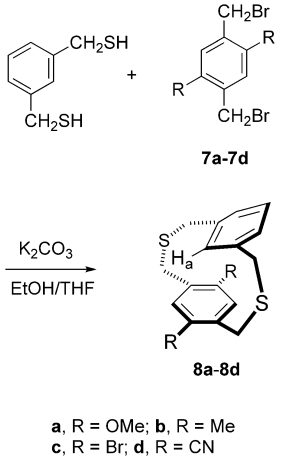
Table 2. Experimental energy barriers for the topomerization process in compounds **1** and **4a–4d**.

Substituent	Compound	$\Delta G^{\neq}$ [kJ mol^{-1}][a]
NH_2	**4d**	23.1
OMe	**4c**	22.6
H[b]	**1**	22.0
CN	**4b**	22.5
NO_2	**4a**	22.9

[a] Relative error: (± 0.1) kJ mol^{-1}. [b] The value for compound **1** is slightly different from that reported in reference [1] (21.7 kJ mol^{-1}) because it was re-determined under conditions identical to those employed for compounds **4a–4d**.

From these data, it was clear that even if the substituents encompassed a wide range of electron-donating or electron-withdrawing abilities, the overall variation in barrier energies was very small (1.1 kJ mol^{-1}). In addition, and contrary to expectations based on the polar/π-rationale, there was no apparent correlation between the energy barriers and the electronic nature of the substituents: the energy barrier showed a minimum value for H-substituted compound **1**, an intermediate value for the NC- (**4b**) and MeO-substituted (**4c**) adducts, and and a maximum value for the NO_2- and NH_2-substituted derivatives (**4a** and **4d**, respectively). It must be noted that, within the framework of the polar/π-rationale, these latter two compounds were expected to afford the highest and the lowest barriers, respectively. Moreover, when the energy barriers were plotted against the Hammett σ_{para} parameters of the substituents, an irregular V-shaped curve was obtained, in which the values for the two electron-donating and the two electron-withdrawing substituents faced each other in pairs (amino/nitro, methoxy/cyano) at virtually identical energy levels and the value for the unsubstituted compound corresponded to a minimum.

Puzzled by these results, we prepared a series of compounds in which the availability of the π-electrons of the platform ring was systematically changed by the introduction of different substituents. These substituents were located on both sides of the ring, both for synthetic convenience and to provide an equal steric bias for the front and back sides of the top ring, thereby avoiding the occurrence of sterically preferred conformations. By using the usual synthetic approach (Scheme 4), the reaction of (2R,5R)-substituted-1,4-bis(bromomethyl)benzenes **7a–7d** with 1,3-bis(mercaptomethyl)benzene afforded cyclophanes **8a–8d** in 40–78% yield after purification by column chromatography on silica gel and crystallization. The crystal structures of these compounds (see the Experimental Section and the Supporting Information) showed the expected moderately tilted disposition of the rings, with interplanar angles of 14.7, 19.4, 16.7, and 5.5° for adducts **8a–8d**, respectively.



Scheme 4. Synthesis of 2,11-dithia[3,3]-metaparacyclophanes **8a–8d**.

The fact that these angles were similar to those observed for compounds **4a–4d** could be taken as an indication that the presence of the substituents on the platform ring did not exert a strong steric influence on the structures of these metaparacyclophanes.

As in the case of adducts **4a–4d**, the 400 MHz ^{1}H NMR data (RT, $CDCl_3$; Table 3) confirmed that the H_a atom of the top rings of compounds **8a–8d** was located within the shielding cone of the benzene platform.

Table 3. Chemical shifts of the H_a atom in compounds **1** and **8a–8d**.

Substituent	Compound	δ H_a [ppm]	$\Delta\delta$ [ppm][a]
OMe	**8a**	5.80	1.46
Me	**8b**	5.63	1.61
H	**1**	5.60	1.64
Br	**8c**	5.88	1.36
CN	**8d**	5.74	1.50

[a] Chemical-shift difference between the H_b proton in 1,3-bis(methylthiomethyl)benzene (**5**; $\delta = 7.24$ ppm) and the H_a proton in compounds **1** and **8a–8d**.

Indeed, the resonance of the H_a atom was shifted upfield with respect to that of the corresponding proton of 1,3-bis(methylthiomethyl)benzene (**5**; $\delta = 7.24$ ppm). However, as with compounds **4a–4d**, no direct correlation was observed for adducts **8a–8d** between the upfield shift and the electronic nature of the substituents.

Next, under the experimental conditions described above, 600 MHz ^{1}H VT-NMR experiments were performed to determine the barrier to topomerization for compounds **8a–8d**. Consistent with the hypothesis of a freely occurring ring-flipping process and with the symmetry of these derivatives, the spectra of compounds **8a–8d** showed two AB systems for the methylene protons of the CH_2-S-CH_2 bridges from room temperature down to −120 °C. On further lowering the temperature, these signals broadened and eventually split into separate signals that corresponded to four AB systems, which arose from the diastereotopicity of the H atoms of each methylene group. Therefore, eight exchanging doublets had to be simulated. This spin system was encoded in the DNMR6 program as two sets of two exchanging conformations with four chemical shifts each (an example of the input file is reported in the Supporting Information).

The same sets of spectra were recorded for all the compounds at seven different temperatures, and the exact temperature of each spectrum was checked by using the line width of dimesityl ketone. Small variations in the dial temperature (less than ±1.0 °C) were necessary in some cases to match the correct line shape of the internal temperature standard. The line-shape simulations obtained at −149.5 °C for compounds **8a–8d** are shown in Figure 1 (two similar sets of spectra along with all other spectra, as well as the corresponding simulations, are given in the Supporting Information). The values of the rate constants at various temperatures are given in Table 4. For a better comparison, the

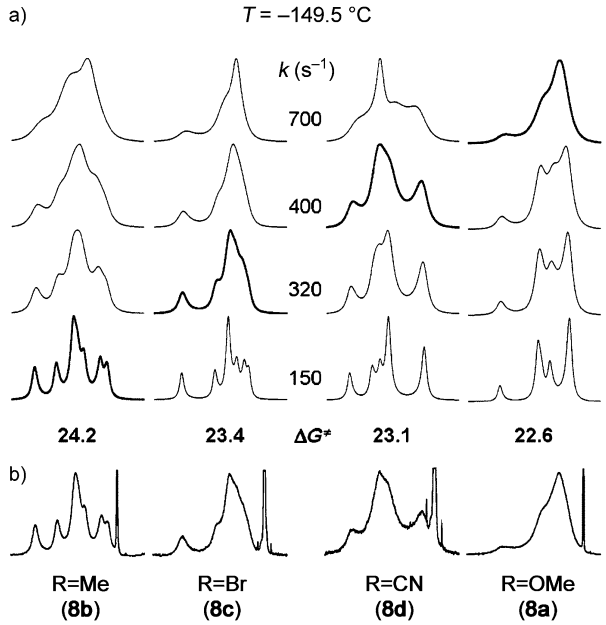


Figure 1. a) Line-shape simulations. In each column, the bold trace shows the best simulation of the experimentally determined spectrum, together with the corresponding rate constant. The other three traces in each row show the simulations for the other three compounds obtained by using the rate constant from the bold traces. b) Experimental spectra taken at −149.5 °C for compounds **8a**–**8d**.

Table 4. Rate constants k [s^{-1}] and free-energy barriers (in parentheses [kJ mol^{-1}]) obtained by VT-NMR spectroscopy for compounds **8a**–**8d**.

T [°C][a]	**8a** R = OMe[b]	**8b** R = Me[b]	**8c** R = Br[b]	**8d** R = CN[b]
−129.5	15000	5000	9000	10000
	(22.8)	(24.1)	(23.4)	(23.3)
−140.0	3500	1080	2100	2400
	(22.6)	(24.0)	(23.2)	(23.1)
−145.0	1550	370	760	1020
	(22.6)	(24.1)	(23.4)	(23.1)
−149.5	700	150	320	400
	(22.6)	(24.2)	(23.4)	(23.1)
−152.5	370	80	170	240
	(22.7)	(24.2)	(23.4)	(23.1)
−155.5	170	50	90	130
	(22.8)	(24.0)	(23.5)	(23.1)
−162.0	< 50	< 25	< 25	< 50
mean value[c]	22.7	24.1	23.4	23.1
	(0.1)	(0.1)	(0.1)	(0.1)

[a] Standardized with dimesityl ketone (see text). [b] The $\Delta G^{\neq}$ values were obtained by using the Eyring equation. [c] Standard deviations are given in parentheses.

experimental energy barriers for the topomerization process in compounds **1** and **8a**–**8d** are shown in Table 5.

In commenting on these data, it must be pointed out that, as for the previous set of compounds, unsubstituted adduct **1** showed the lowest energy barrier and the introduction of two substituents on the platform ring consistently resulted in higher energy barriers (minimum variation: +0.7 kJ mol^{-1} for MeO-substituted compound **8a**, maximum variation:

Table 5. Experimental energy barriers for the topomerization process in compounds **1** and **8a**–**8d**.

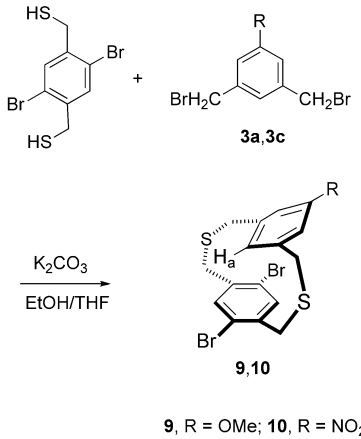
Substituent	Compound	$\Delta G^{\neq}$ [kJ mol^{-1}][a]
OMe	**8a**	22.7
Me	**8b**	24.1
H	**1**	22.0
Br	**8c**	23.4
CN	**8d**	23.1

[a] Relative error: ±0.1 kJmol^{-1}.

+2.1 kJ mol^{-1} for Me-substituted derivative **8b**). However, no apparent correlation was observed between the trend in the energy barriers and the steric bulk of the substituents (A values: MeO 0.60, Me 1.70, Br 0.38, CN 0.17; B values: MeO 5.6, Me 7.4, Br 8.7, CN 5.9).[16]

As for a possible electronic effect, the observed variation in the energy barriers did not appear to be linearly related to the electron-donating or -withdrawing nature of the substituents. Within the framework of the polar/π-model, an electron-richer platform ring was expected to provide a stronger destabilization of the GS of these adducts (because of a stronger repulsion with the top ring), and hence a lower barrier. The data for compounds **8a**–**8d** seemed to confirm that the behavior of these metaparacyclophanes, as for compounds **4a**–**4d**, could not be rationalized on the basis of the polar/π effect.[5]

Next, we investigated the effect of the combined presence of substituents on both the top and platform rings. We prepared a third series of compounds by using the usual approach (Scheme 5). Reaction of 2,5-dibromo-1,4-bis(mercaptomethyl)benzene with 1,3-dibromomethyl-benzenes **3a** and **3c** afforded adducts **9** and **10** in 74 and 67% yield, respectively. The crystal structures of these compounds (see the Experimental Section and the Supporting Information) showed interplanar angles of 17.3 and 12.9° for adducts **9** and **10**, respectively.



Scheme 5. Synthesis of 2,11-dithia[3,3]-metaparacyclophanes **9** and **10**.

As for the other metaparacyclophanes reported herein, the ^{1}H NMR data (400 MHz, RT, $CDCl_3$) confirmed that the H_a atom of the top ring of compounds **9** and **10** was located within the shielding cone of the dibromo-substituted benzene platform ($\delta = 5.46$ and 6.23 ppm, respectively).

When the barriers to topomerization were determined by 600 MHz ^{1}H VT-NMR experiments carried out under the carefully controlled conditions described above, $\Delta G^{\neq}$ values of 23.6 and 25.3 kJ mol^{-1} were obtained for adducts **9** and **10**, respectively. For sake of comparison, these data are reported in Table 6 along with those of adducts **8c** (no substituent in top ring and dibromo-substitution in the platform ring), **4c**, **1**, and **4a** (same substituents in the top ring as compounds **9**, **8c**, and **10**, respectively, and no substituents in the platform ring).

Table 6. Experimental energy barriers for the topomerization process in compounds **8c**, **9**, and **10**.

Substituent[a]	Substituent[b]	Compound	$\Delta G^{\neq}$ [kJ mol^{-1}][c]	Substituent[b]	Compound	$\Delta G^{\neq}$[c]	$\Delta\Delta G^{\neq}$[d]
OMe	Br	**9**	23.6	H	**4c**	22.6	+1.0
H	Br	**8c**	23.4	H	**1**	22.0	+1.4
NO_2	Br	**10**	25.3	H	**4a**	22.9	+2.4

[a] Substituent on the top ring. [b] Substituent on the platform ring. [c] Relative error: ($\pm$0.1) kJ mol^{-1}. [d] Difference in $\Delta G^{\neq}$ values for the **9**/**4c**, **8c**/**1**, and **10**/**4a** pairs, respectively.

Once again, the data for compounds **8c**, **9**, and **10** showed no correlation between the barrier values and the electron-donating or -withdrawing nature of the substituent on the top ring, as was the case for the previous series of compounds (for an immediate comparison, see for instance the trend in barrier values for adducts **4c**, **1**, and **4a**, Table 5). By comparing the two sets of data, dibromo-substitution on the platform ring induced a slight increase in the energy barrier in the case of the methoxy-substituted compounds, and this increase became larger as the top ring was made less and less electron rich (Table 6).

Even if this latter observation could be rationalized on the basis of the polar/π-effect,[5] for which a diminished electron density on both interacting rings (as in compound **10**) should results in a more favorable (less-repulsive) interaction in the GS, and hence in a higher barrier,[17] we must note that most of the experimental results collected in this work could not be reconciled with this rationalization.

After the pioneering studies by Hunter and Sanders,[5a,b] and Jorgensen and Severance,[8f] several theoretical investigations have been carried out with the aim of understanding the nature of the interactions between face-to-face-oriented substituted benzenes, and to explain the relative stability of these dimers.[2] In particular, recent computational studies[18] suggested that, in the gas phase, both electron-donating- and electron-withdrawing substituents increase the attraction between two benzene rings in an idealized face-to-face orientation.[18a] In a very recent article, Sherrill and co-workers proposed that charge-penetration (an attractive electrostatic interaction that arises from the overlap of the electron densities of the two monomers) could explain the surprising favorable interaction predicted by calculations for benzene dimers that carry both electron-donating- and electron-withdrawing substituents.[18g] This effect should result from a favorable electrostatic (Coulombic) component of the intramolecular attraction. Sherrill and co-workers also indicated that charge-penetration effects could be important when the distance between the interacting rings is about 4 Å or less, a distance very similar to the one observed between the arenes of our metaparacyclophanes.[18 g]

This theoretical work seems to correctly predict the trend in the barriers that we observed experimentally for our metaparacyclophanes. Indeed, in all three series studied, the barrier was at its minimum value when one or both of the interacting rings did not carry any substituents, whilst higher values were observed for both electron-donating and electron-withdrawing mono- or poly-substituted compounds. Because we considered a higher barrier value to be an indication of the higher stability of the GS conformation in which the aromatic rings faced each other, we concluded that the rationalization reported by Sherrill and co-workers[18g] could be used to tentatively explain our experimental results. Still, it must be emphasized once again that the effect exerted by widely different substituents on the interaction, as gauged by the determination of the barrier to topomerization for our cyclophanes, even if experimentally significant, remained small and any possible rationalization of this effect must be adopted cautiously.

In concluding this discussion, it seems appropriate to make some considerations on the scientific significance of using theoretical predictions to rationalize experimental results obtained with model systems. In this particular case, one is left wondering why different rationalizations seem to nicely explain the short-distance, face-to-face interaction between substituted benzenes only within the boundaries of a given model system (for instance, the polar/π-effect[5] in the case of 1,8-diarylsubstituted naphthalenes,[17] and the charge-penetration effect[18g] for the metaparacyclophanes investigated in this work). A realistic (but possibly indulgent) answer is that an effort in finding a good-for-all-models rationalization is intrinsically bound to fail because even the best and more-general rationalization cannot remain unaffected by the structural requirements and steric bias of the model system. A less-comforting (but more stimulating) answer calls for a (still-inadequate) knowledge of the relative importance of the fundamental factors that rule the aromatic–aromatic interaction, and a lack in the researcher's imagination in designing the "ideal" model system.

Conclusion

In conclusion, three series of 2,11-dithia[3,3]-metaparacyclophanes were designed and synthesized to study the effect of substituents on the intramolecular aromatic–aromatic interactions between partially overlapped and slightly tilted face-to-face-oriented benzene rings. The X-ray structures of these compounds showed interplanar distance of about 3.5 Å and interplanar angles ranging from 5 to 19°. Topomerization of these derivatives occurred by flipping of the *meta*-substituted ring over the *para*-substituted one, a process in which the two rings adopted a continuum of edge-to-face dispositions, including an orthogonal one, which were less-stable than the starting arrangement. The barriers to the isomerization process were experimentally determined by VT-NMR spectroscopy, by using an internal temperature standard to safely assess even minor differences in energy (estimated relative experimental error: ± 0.1 kJ mol^{-1}). The variation of the barriers as a function of the different substitution on the interacting ring was small but still significant given the high degree of accuracy obtained in their experimental assessment. The observed trend in the barriers could not be rationalized on the basis of electrostatic and polarity considerations that worked nicely with other model systems.[5,17] An alternative theoretical explanation that suggested a role for a charge-penetration effect[18g] seemed to provide a qualitative rationalization of these experimental results.

Experimental Section

General: All manipulations were carried out under a nitrogen atmosphere by using standard Schlenk techniques, unless otherwise stated. Compounds **3a**,[19] **3b**,[20] **3c**,[21] 1,3-bis(mercaptomethyl)benzene,[22] **7a**,[23] **7d**,[24] and 2,5-dibromo-1,4-dimercaptomethylbenzene[25] were prepared according to literature procedures. Commercially available compounds **7b**, **7c**, and other chemicals and solvents were used without further purification. Elemental analysis (C, H, N) was performed by the Microanalytical Services, College of Chemistry, CCNU. ^{1}H NMR and ^{13}C NMR spectroscopy was performed on a Varian Mercury Plus 400 spectrometer operating at 400 and 100.6 MHz, respectively. Chemical shifts are relative to TMS. Mass spectra were obtained on a Finnigan Trace mass spectrometer.

General procedure for the synthesis of compounds 4a–4c: A solution of equimolar amounts of 1,4-dimercaptomethylbenzene and dibromide **3a**–**3c** in THF (300 mL) was added dropwise under a N_2 atmosphere over 12 h to a solution of K_2CO_3 (5 equiv) that was heated to reflux in EtOH (1 L). After an additional 2 h of heating to reflux, the mixture was cooled and the solvents were removed under vacuum. To the resulting residue, CH_2Cl_2 (100 mL) and water (100 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed, and the resulting solid was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 1:1, v/v) to give the target compounds, which were further purified by recrystallization from toluene. Single crystals suitable for X-ray diffraction were obtained by the layer diffusion of CH_2Cl_2 into *n*-hexane.

Compound 4a (1^5-nitro-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) was obtained from the reaction of compound **3a** (2.32 g, 7.5 mmol) and 1,4-dimercaptomethylbenzene (1.28 g, 7.5 mmol) as a white solid in 49% yield (1.16 g). M.p. +163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.50$ (s, 4H; CH_2), 3.86 (s, 4H; CH_2), 5.96 (s, 1H; ArH), 6.90 (s, 4H; ArH), 7.87 ppm (s, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 34.42, 37.23, 121.84, 129.24, 132.21, 137.23, 142.46 ppm; MS (EI): *m*/*z*: 317.2 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{15}NO_2S_2$: C 60.54, H 4.76, N 4.41; found: C 60.67, H 4.53, N 4.31.

Compound 4b (1^5-cyano-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) was obtained from the reaction of compound **3b** (1.45 g, 5 mmol) and 1,4-dimercaptomethylbenzene (0.85 g, 5 mmol) as a white solid in 56% yield (0.83 g). M.p. +170 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.44$ (s, 4H; CH_2), 3.84 (d, J(H,H) = 2.4 Hz, 4H; CH_2), 5.85 (s, 1H; ArH), 6.89 (s, 4H; ArH), 7.29 ppm (s, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.36$, 37.22, 112.15, 118.90, 129.22, 130.45, 130.91, 137.16, 141.92 ppm; MS (EI): *m*/*z*: 297.08 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{15}NS_2$: C 68.65, H 5.08, N 4.71; found: C 68.76, H 4.82, N 4.63.

Compound 4c (1^5-methoxy-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacycloocta-phane) was obtained from the reaction of compound **3c** (1.47 g, 5 mmol) and 1,4-dimercaptomethylbenzene (0.85 g, 5 mmol) as a white solid in 56% yield (0.85 g). M.p. +153 °C); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.41$ (s, 4H; CH_2), 3.76 (s, 3H; CH_3), 3.84 (s, 4H; CH_2), 5.23 (s, 1H; ArH), 6.53 (s, 2H; ArH), 6.91 ppm (s, 4H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 35.19$, 37.44, 55.22, 112.18, 120.40, 129.09, 129.11 (d, $J =$ 2.2 Hz), 137.20, 141.59, 159.60 ppm; MS (EI): *m*/*z*: 302.11 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{18}OS_2$: C 67.51, H 6.00; found: C 67.72, H 5.79.

Synthesis of compound 4d: (1^5-amino-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) $H_2NNH_2{\cdot}H_2O$ (5 mL) was added slowly to a stirring mixture of $FeCl_3$ (0.10 g, 0.6 mmol), active carbon (0.5 g), and compound **4a** (0.54 g, 1.70 mmol) in DMF (30 mL) at RT. After the addition was complete, the reaction mixture was stirred at +80 °C for 3 h. The mixture was then cooled at RT and filtered through a layer of Celite; water was added to quench the reaction. The filtrate was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were washed with water, dried, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 2:1, v/v) to give compound **4d** (0.43 g, 88%) as a white solid. M.p. +77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.35$ (s, 4H; CH_2), 3.52 (s, 2H; NH_2), 3.83 (s, 4H; CH_2), 5.03 (s, 1H; ArH), 6.30 (s, 2H; ArH), 6.93 ppm (s, 4H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 35.12$, 37.48 (CH_2), 113.46, 118.74, 129.10 (t, $J = 2.3$ Hz), 137.19, 141.28, 146.25 ppm (ArC); MS (EI): *m*/*z*: 287.3 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{17}NS_2$: C 66.86, H 5.96, N 4.87; found: C 66.95, H 5.73, N 5.01.

General procedure for the synthesis of compounds 8a–8d: A solution containing equimolar amounts of 5-di(*R*)-substituted-1,4-bis(bromomethyl)benzenes **7a**–**7d** and 1,3-bis(mercaptomethyl)benzene in THF (300 mL) was added dropwise under a N_2 atmosphere over 12 h to a solution of K_2CO_3 (5 equiv) that was heated to reflux in EtOH (1 L). After a further 2 h of heating to reflux, the mixture was cooled and the solvents were removed under vacuum. To the resulting residue, CH_2Cl_2 (100 mL) and water (100 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed, and the resulting solid was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 1:1, v/v) to give the target compounds, which were further purified by recrystallization from toluene.

Compound 8a (5^2,5^5-dimethoxy-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) was obtained from the reaction of 1,3-bis(mercaptomethyl)benzene (0.68 g, 4 mmol) and compound **7a** (1.30 g, 4 mmol) as a white solid in 65% yield (0.87 g). M.p. +150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.50$ (d, J(H,H) = 12.8 Hz, 6H; CH_2), 3.61 (s, 6H; OCH_3), 4.23 (d, J(H,H) = 12.8 Hz; 2H), 5.80 (s, 1H; ArH), 6.45 (s, 2H; ArH), 7.00 (d, J(H,H) = 7.2 Hz, 2H; ArH), 7.12 ppm (t, J(HH) = 7.2 Hz, 1H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.02$, 35.13, 55.82, 113.50, 126.17, 126.49, 127.08, 127.68, 139.80, 151.36 ppm; MS (EI): *m*/*z*: 332.10 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{20}O_2S_2$: C 65.02, H 6.06; found: C 65.25, H 5.98.

Compound 8b (5^2,5^5-dimethyl-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) was obtained from the reaction of 1,3-bis(mercaptomethyl)benzene (0.6 g, 3.5 mmol) and compound **7b** (1.02 g, 3.5 mmol) as a

white solid in 40% yield (0.42 g). M.p. +128°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 6H; CH_3), 3.45 (q, J(H,H) = 16 Hz, 4H; CH_2), 3.69 (d, J(H,H) = 13.2 Hz, 2H; CH_2), 3.94 (d, J(H,H) = 13.2 Hz, 2H; CH_2), 5.63 (s, 1H; ArH), 6.68 (s, 2H; ArH), 6.98 (d, J(H,H) = 7.2 Hz, 2H; ArH), 7.10 ppm (t, J(H,H) = 7.2 Hz, 1H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.67, 34.22, 35.01, 126.44, 126.54, 127.73, 132.04, 133.85, 135.16, 139.40 ppm; MS (EI): m/z: 300.11 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{20}S_2$: C 71.95, H 6.71; found: C 71.86, H 6.81.

Compound 8c (5^2,5^5-dibromo-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) was obtained from the reaction of 1,3-bis(mercaptomethyl)benzene (1.70 g, 10 mmol) and compound **7c** (4.22 g, 10 mmol) as a white solid in 53% yield (2.28 g). M.p. +175°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55 (q, J(H,H) = 15.2 Hz, 4H; CH_2), 3.72 (d, J(H,H) = 13.6 Hz, 2H; CH_2), 4.15 (d, J(H,H) = 13.2 Hz, 2H; CH_2), 5.88 (s, 1H; ArH), 7.09 (d J(H,H) = 8 Hz, 2H; ArH), 7.18–7.22 ppm (m, 3H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.83, 35.84, 123.12, 126.03, 127.39, 128.45, 135.03, 138.16, 139.11 ppm; MS (EI): m/z: 430.2 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{14}Br_2S_2$: C 44.67, H 3.28; found: C 44.76, H 3.06.

Compound 8d (5^2,5^5-dicyano-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) was obtained from the reaction of 1,3-bis(mercaptomethyl)benzene (0.68 g, 4 mmol) and compound **7d** (1.26 g, 4 mmol) as a white solid in 78% yield (1.0 g). M.p. +252°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 4H; CH_2), 3.86 (d, J(H,H) = 13.2 Hz, 2H; CH_2), 4.19 (d, J(H,H) = 14.8 Hz, 2H; CH_2), 5.74 (s, 1H; ArH), 7.18 (d, J(H,H) = 7.6 Hz, 2H; ArH), 7.28 (t, J(H,H) = 7.6 Hz, 1H; ArH), 7.36 ppm (s, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.06, 35.31, 115.72, 116.21, 125.80, 128.09, 129.25, 134.38, 139.18, 142.13 ppm; MS (EI): m/z: 322.10 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{14}N_2S_2$: C 67.05, H 4.38, N 8.69; found: C 67.24, H 4.07, N 8.65.

Synthesis of compounds 9 and 10: The procedure for the synthesis of compounds **9** and **10** was similar to that employed for compounds **4a**–**4c** and **8a**–**8d**.

Compound 9 (1^5-methoxy-5^2,5^5-dibromo-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) was obtained from the reaction of 2,5-dibromo-1,4-dimercaptomethylbenzene (3.28 g, 10 mmol) and compound **3c** (2.94 g, 10 mmol) as a white solid in 74% yield (3.41 g). M.p. +218°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (q, J(H,H) = 15.2 Hz, 4H; CH_2), 3.71 (d, J(H,H) = 13.2 Hz, 2H; CH_2), 3.81 (s, 3H; OCH_3), 4.14 (d, J-(H,H) = 13.2 Hz, 2H; CH_2), 5.51 (s, 1H; ArH), 6.67 (s, 2H; ArH), 7.20 ppm (s, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.90, 35.77, 55.31, 113.15, 119.32, 123.12, 135.06, 138.10, 140.51, 159.53 ppm; MS (EI): m/z: 460.3 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{16}Br_2OS_2$: C 44.36, H 3.50; found: C 44.54, H 3,31.

Compound 10 (1^5-nitro-5^2,5^5-dibromo-3,7-dithia-1(1,3)-benzena-5(1,4)-benzenacyclooctaphane) was obtained from the reaction of 2,5-dibromo-1,4-dimercaptomethylbenzene (3.28 g, 10 mmol) and compound **3a** (3.09 g, 10 mmol) as a white solid in 67% yield (3.18 g). M.p. +211°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (q, J(H,H) = 15.6 Hz, 4H; CH_2), 3.74 (d, J(H,H) = 13.2 Hz, 2H; CH_2), 4.16 (d, J(H,H) = 13.2 Hz, 2H; CH_2), 6.23 (s, 1H; ArH), 7.22 (s, 2H; ArH), 8.02 ppm (s, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.21, 35.66, 122.71, 123.26, 131.54, 135.19, 135.59, 138.26, 141.43 pm; MS (EI): m/z: 475.2 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{13}Br_2NO_2S_2$: C 40.44, H 2.76, N 2.95; found: C 40.65, H 2.56, N 2.84.

Variable-temperature NMR spectroscopy: Samples of the compounds were prepared in $CDCl_3$ by adding a concentrated stock solution of dimesityl ketone in $CDCl_3$ to the compounds until a 6:1 molar ratio was obtained. The solutions were transferred into the NMR tubes that had been adapted for variable-temperature experiments (Wilmad 507PP with a sealed Pyrex pipe to allow the connection to a vacuum line). After evaporation of the solvent by a stream of nitrogen, the NMR tubes were manipulated with a vacuum line. The NMR tubes were evacuated and immersed in liquid nitrogen to condense consecutively $CDFCl_2$ (0.40 mL)[26] and CHF_2Cl (0.2 mL), which were transferred as gases from lecture bottles. The resulting 2:1 (v/v) mixture remained fluid down to −175°C. The tubes were subsequently sealed under reduced pressure (0.01 Torr) by using a methane/oxygen torch. Avoiding any rapid temperature changes, the tubes were cautiously warmed to ambient temperature, at which a pressure of about 8 atm had developed inside the sample. (Caution: risk of explosion if the samples are heated above 30°C) After having been kept at ambient temperature for 24 h, the samples were safely introduced into the probe head of the spectrometer, which had already been cooled to −30°C.

VT-NMR spectra were recorded on an INOVA spectrometer operating at 14.4 T (600 MHz for ^{1}H), by using a customized VT probe (Nalorac, CA) and a preconditioning unit (FTS). When operating the spectrometer at temperatures below −100°C, a flow of dry nitrogen was first passed through the preconditioning unit, which was adjusted to −50°C. Then, the gas was entered into an inox steel heat-exchanger that was immersed in liquid nitrogen and connected to the probe head by a vacuum-insulated transfer line, which was further insulated by neoprene foam. The gas flow was increased on lowering the temperature from 10 to 30 L min^{-1}, and it was measured by using a flow meter to reproduce the same gas flow for all of the samples at a certain temperature. All of the spectra were recorded on samples that were not spinning to avoid any uncontrollable effects of the bearing and the spinning flows on the internal temperature of the sample, and because all of the temperature calibrations were taken under these conditions. A spinner designed for variable-temperature experiments was used (Rototec NS). This spinner allows part of the cooling gas to flow through the internal hole of the spinner and around the part of the NMR sample that was inside the spinner to reduce the temperature gradients that create convective motions inside the sample along the z axis. The temperature was left to stabilize for about 10–15 min before the acquisition of any spectra. The samples were carefully shimmed at all of the temperatures by monitoring the solvent lines (CHF_2Cl and acetone traces inside the $CDFCl_2$) and by checking the *para*-methyl signal of the mesithyl ketone, to reproduce the same linewidths in all of the samples at the various temperatures. Temperature calibrations were performed before the experiments, by using a digital thermometer (Comark KX) and a Cu/Ni thermocouple immersed in a dummy sample tube filled with isopentane under identical conditions to those used during the experiments. The uncertainties in the temperatures over the required range (−120 to −170°C) was estimated from the calibration curve to be (±1)°C. Small variations of the dial temperature (less than 1°C) were occasionally required to match the correct line width of mesityl ketone.

The line-shape simulations were performed by means of a PC version of the QCPE program DNMR no. 633, Indiana University (Bloomington, IN).[27] Electronic superimposition of the experimental spectrum and the simulated one enabled the determination of the most-reliable rate constant. The rate constants obtained at various temperatures afforded the free energy of activation by applying the Eyring equation. In all cases, the $\Delta G^{\neq}$ value was found to be invariant over the given temperature range, thus implying a negligible activation entropy ($\Delta S^{\neq}$).

Calculations: Conformational searches were performed by Molecular Mechanics (MMFF force Field as implemented in Titan 1.0.5, Wavefunction inc.). Final geometry optimizations were carried out at the B3LYP/6–31+G(2d,p) level[28] and at the ωB97X-D/6–311++G(2d,p) level[29] by means of the Gaussian 09 series of programs[30] (see the Supporting Information). The standard algorithm in redundant internal coordinates and the default criteria of convergence were employed in all of the calculations. Harmonic vibrational frequencies were calculated for all of the stationary points. For each optimized ground state, the frequency analysis showed the absence of imaginary frequencies.

Crystal data: Single-crystals with appropriate dimensions was mounted on a glass fiber for the diffraction experiments. Intensity data were collected on a Nonius Kappa CCD diffractometer with $Mo_{K\alpha}$ radiation (0.71073 Å) at RT. The structures were solved by a combination of direct methods (SHELXS-97[31]) and Fourier difference techniques and refined by full-matrix least-squares (SHELXL-97[32]). All non-H atoms were refined anisotropically. The hydrogen atoms were placed in the ideal positions and refined as riding atoms. CCDC-852964 (**4a**), CCDC-852965 (**4b**), CCDC-852966 (**4c**), CCDC-852967 (**4d**), CCDC-852968 (**8a**), CCDC-852969 (**8b**), CCDC-852970 (**8c**), CCDC-852971 (**8d**), CCDC-852972 (**9**), and CCDC-852973 (**10**) contain the supplementary crystallo-

graphic 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.

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[8] The C_{Ar}–H/π-interaction has been explained both by using the polar/π-rationale (for example, see: a) F. J. Carver, C. A. Hunter, D. J. Livingstone, J. F. McCabe, E. M. Seward, *Chem. Eur. J.* **2002**, *8*, 2847–2859; b) W. B. Jennings, B. M. Farrell, J. F. Malone, *J. Org. Chem.* **2006**, *71*, 2277–2282; c) G. A. Breault, C. A. Hunter, P. C. Mayers, *J. Am. Chem. Soc.* **1998**, *120*, 3402–3410; d) S. L. Cockroft, C. A. Hunter, *Chem. Commun.* **2006**, 3806–3808; e) S. L. Cockroft, C. A. Hunter, *Chem. Commun.* **2009**, 3961–3963) and by using alternative interpretations (for example, see: f) W. J. Jorgensen, D. L. Severance, *J. Am. Chem. Soc.* **1990**, *112*, 4768–4774; g) S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497–4498; h) E. Kim, S. Paliwal, C. S. Wilcox, *J. Am. Chem. Soc.* **1998**, *120*, 11192–11193). However, given the fact that the edge-to-face conformations for the cyclophanes considered herein were considerably less-stable (and thus far-less populated) than the tilted face-to-face dispositions, for the sake of simplicity in our rationalization we considered that the contribution of a C_{Ar}–H/π-interaction to the overall interaction was negligible. Obviously, a combination of two effects can occur, but the relative importance of the single contributions is difficult to assess.

[9] For a recent discussion, see: D. Casarini, L. Lunazzi, A. Mazzanti, *Eur. J. Org. Chem.* **2010**, 2035–2056.

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[11] For an example of the use of this technique, see: D. Casarini, S. Grilli, L. Lunazzi, A. Mazzanti, *J. Org. Chem.* **2004**, *69*, 345–351.

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[15] Particular care was taken in preparing identical samples, by using exact volumes of freons (0.40 mL of $CDFCl_2$, 0.20 mL of CHF_2Cl), identical concentrations (2–4 mg of compound, depending on the molecular weight), and the same model of NMR tube (Wilmad 507pp-7, with an added Pyrex pipe to be sealed by a torch).

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