



# Substituent effect on inter-ring interaction in paracyclophanes

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Received: 1 November 2018 / Accepted: 2 February 2019 / Published online: 19 February 2019  
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## Abstract

The theoretical calculations, namely multipole-derived charge analysis, quantum theory of atom in molecules, and non-bonding interaction (NCI), were performed for [2.2]paracyclophanes, [2.2]paracyclophane-7,9-dienes, and [3.3]paracyclophanes optimized at B3LYP/6-311++G\*\* level, including dispersion correction. The substituent effect of the electron donor N(Me)<sub>2</sub> and electron acceptor NO<sub>2</sub> group and the influence of the length of bridges joining the aromatic ring on aromatic ring interaction energy (AIE) and strain energy were discussed. The local and electrostatic character of the substituent effect in paracyclophanes was shown. The presence of the weak orbital through-space C...C interaction between the [3.3]paracyclophane ring and weak CH...O hydrogen bonds between the substituents in the different rings was shown.

**Keywords** [2.2]Paracyclophane · [2.2]Paracyclophane-7,9-dienes · [3.3]Paracyclophanes QTAIM · NCI · AIE · SE

## Introduction

[2.2]Paracyclophanes have attracted interest for more than 20 years, and this interest has not abated yet. Due to their electronic properties and rigid structure, [2.2]paracyclophanes have found an application in manifold branches of chemistry and technology. As an example, let us mention the designing of optoelectronic materials [1, 2], materials for photonics and electronics [3], catalysts in polymer synthesis [4], synthesis of chiro-optically active compounds [5, 6], as well as in biology and medicine [7] or supramolecular chemistry [8]. One of the important challenges is the synthesis of new functionalized [2.2]paracyclophanes and the investigation of the substituents' influence on their chemical, electronic, and structural properties [3].

The crucial problem is to understand the nature of through-space interaction in [2.2]cyclophanes and the

substituents' influence on this interaction. Studies of the isolated cyclophanes permit the investigation of the nature of interactions in the ground state and may be helpful in understanding the role of an interaction in more complex systems. The  $\pi$ - $\pi$  stacking interaction between the aromatic rings in [2.2]paracyclophane [9–12] and its complexes [13] was the subject of theoretical investigations, but it has not been fully explained. Close proximity of two aromatic rings of [2.2]cyclophane leads to repulsive as well as attractive interaction between the  $\pi$  electrons of both aromatic rings. By analogy with the widely investigated benzene dimers [11, 14–17], the energy of the  $\pi$ - $\pi$  interaction between the paracyclophane aromatic rings may be presented as a sum of electrostatic, dispersive, orbital interactions and the Pauli repulsion contribution. For benzene dimers, the dispersion was shown to be the dominant attractive contribution to the binding energy.

Lysenko et al. [10], using the AIM analysis, evidenced that the charge-transfer interaction in [2.2]paracyclophane did not occur. Caramori and Galembeck [9] applied the NBO, MOs, and AIM analysis to investigate [2.2]paracyclophane and *trans* and *cis* [2.2]methacyclophanes. The NBO analysis showed the presence of a significant through-space interaction involving the occupied and unoccupied orbitals ( $\pi$ - $\pi^*$ ) in [2.2]metacyclophane. It is only for this compound that the AIM method confirmed the existence of the through-space interaction between different metacyclophane rings. The authors [9, 10] have not considered

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s11030-019-09926-7>) contains supplementary material, which is available to authorized users.

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other attractive through-space interactions. Kamyra and Muchall [18] studied the structure and inter-ring interactions for several cyclophanes. He assumed that the attractive through-space interaction was controlled by dispersion and electrostatic interaction and, for the shorter distance, the exchange–repulsion dominated. The author showed that the explicit account of the electron correlation effects between the two aromatic rings is crucial for a correct description of the structures of cyclophanes. He named this interaction the “overlap-dispersive,” to differentiate it from the classical dispersion (van der Waals) interactions. Recently, Grimme and Mück-Lichtenfeld [12] calculated the aromatic interaction energies (AIE) and strain energies (SE) for some [2.2] para- and [2.2]metacyclophanes and some other cyclophanes which possessed greater aromatic rings. The AIE presents aromatic interaction energy without taking into account the energy of geometric distortion. The strain energy can be obtained in a cycle of homodesmotic reaction, linking the main parts of the molecule.

An influence of the substitution on the structure and nature of  $\pi$ – $\pi$  interaction in optimized molecules of cyclophanes was also investigated in a few papers [13, 18–21], but the problem is still far from being elucidated. This effect was more thoroughly studied for benzene dimers [15, 22–26]. Recently, Watt et al. [25] and Wheeler and Bloom [16] reviewed the discussion and controversies concerning the substituent effect on the non-covalent through-space interactions in benzene dimers. Wheeler and Houk [24] proposed a local, direct interaction model. The substituent effect was dominated by electrostatic interaction of the local dipoles associated with the substituent and the electric field of another ring [16, 25]. The mesomeric effect of the substituent on the  $\pi$ -electron density was present but was not responsible for substituent effects in benzene dimers. It is noteworthy that the historically first, Hunter and Sanders', electrostatic model [26] explained the substituent effect by the polarization of the  $\pi$ -electron system depending on the electronic properties of the substituent. The analysis of partitioning energy for substituted benzene showed that the electrostatic and dispersive interaction was the most important attractive contribution to the binding energy [15, 16, 24, 25]. Watt et al. [25] found for multi-substituted benzene dimers a fairly good correlation between the calculated energy of the through-space interaction and the sum of the absolute values of the Hammett parameter  $\sigma_m$  describing the inductive/field effects of the substituent ( $\sum|\sigma_m|$ ). The authors showed that the sum of the dispersion, inductive, and exchange contribution to the total binding energy was almost the same for all substituents and the electrostatic energy varied with the substituent according to the  $\sum|\sigma_m|$  values. The results of investigation of the substitution effect in benzene dimers may be helpful in examining this effect in cyclophanes. However, up to now, the results for cyclophanes are rather scant and inconclusive. Frontera et al. investigated the substituent effect on the interaction

energy of [2.2] and [3.3]paracyclophane complexes with  $\text{Na}^+$  and  $\text{Li}^+$  cations. The existence of the through-space substituent effect was evidenced. The electron donating  $\text{NH}_2$  or electron-withdrawing CN substituents in one ring increased or reduced the binding energy of the cations with another ring, respectively. Partitioning the total interaction energy into electrostatic, van der Waals, and polarization contributions showed that the substituent effect on the electrostatic contribution is the most important. The QTAIM analysis confirms the presence of through-space interactions. Caramori and Galembeck [19] analyzed the structure and the through-space interaction in tetrafluoro[2.2] para and metacyclophanes. The existence of the through-space  $\pi$ – $\pi^*$  for metacyclophane orbital interaction was evidenced by the QTAIM analysis. Galembeck and Caramori [20] studied the influence of F, CN, CO,  $\text{NH}_2$  substitution and protonation effects on the geometry and through-space interactions in a series of [2.2]paracyclophanes. The authors showed the influence of substituents on the dihedral angles of bridges and that this effect did not depend on the electronic properties of the substituents. The presence of numerous through-space unstable interactions in the substituted cyclophanes was suggested. Kamyra and Muchall [18] showed the influence of donor–acceptor properties of the substituents on the geometric parameters and the ionization potentials and excitation energies of [ $n.n$ ]paracyclophanes. The existence of the charge-transfer process in the substituted cyclophanes was evidenced.

In the previous paper [21], we investigated interactions between the aromatic rings of a series of [2.2]paracyclophanes using QTAIM and NCI analysis in both crystal structure and optimized [2.2]paracyclophanes with the parallel-displaced aromatic rings and additional bridges, and the existence of the through-space orbital interaction was stated. Contrary to expectation, no influence of the substituent effect on these interactions was observed. It is notable that, as mentioned above, no “classical” substituent effect on the stacking interactions in benzene dimers was present. In order to study the substituent effect on the  $\pi$ – $\pi$  through-space interaction in the paracyclophane more thoroughly, we have undertaken the calculation of energy of aromatic ring interaction AIE and steric strain SE as well as the calculation of the multipole-derived charges on the aromatic ring carbon atoms in a series of optimized [2.2]paracyclophanes, [2.2]paracyclophane-7,9-dienes, and [3.3]paracyclophanes substituted with the electron-withdrawing  $\text{NO}_2$  and electron-donating  $\text{N}(\text{CH}_3)_2$  substituents.

## Computational details

Optimization of the investigated cyclophanes: [2.2]paracyclophanes, [2.2]paracyclophane-7,9-dienes, and [3.3]paracyclophanes and their derivatives with combinations of  $\text{NO}_2$

and  $N(CH_3)_2$  groups was performed at the DFT B3LYP/6-311++G\*\*/DG3 level of calculation including Grimme dispersion [27] using the Gaussian 09 program [28]. The wave functions evaluated for optimized and crystal structure molecules were used as an input to the AIMALL [29] and NCI [30] program. The multipole-derived charge analysis implemented in the ADF program [31, 32] was performed for the molecule optimized with Gaussian without further optimization.

## Results

### Substituent effect on the geometry, AIE, and SE energies for [2.2]cyclophanes, [2.2]cyclophane-1,9-dienes, and [3.3]cyclophanes

The structure of [2.2]paracyclophane was an object of numerous experimental and theoretical studies [10–13, 33, 34]. Recently, Wolf et al. [34] definitely stated that [2.2]paracyclophane below 45 °C crystallizes in a twisted form with an angle of 12.83(4)° and at high temperature in a parallel form. Also the X-ray structure of [2.2]paracyclophane-7,9-diene is known [35], and the heat of formation of this compound was studied. The structure of [3.3]paracyclophane was determined by experimental [36, 37] and theoretical methods [33].

To characterize the conformation of the investigated paracyclophanes, we have used the following parameters: the distance between the benzene rings, the displacement of one aromatic ring relating to another ( $d$  in Scheme 1), and

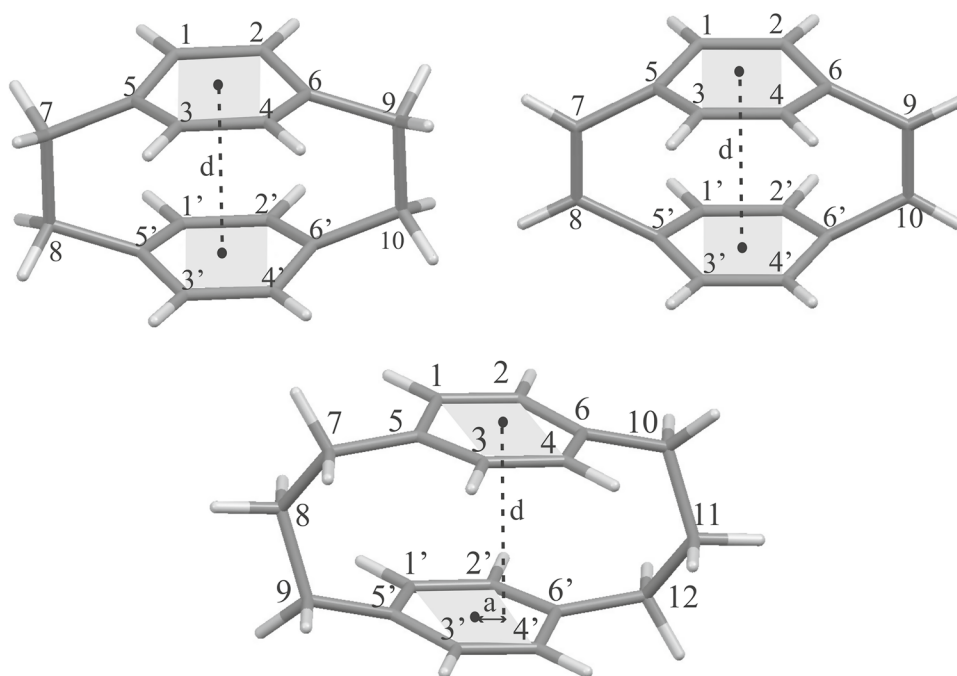
the twist of one ring in relation to another ring (the angle between the gray planes in Scheme 1) [21].

The values of the distance between the rings ( $d$ ), ring displacement ( $a$ ), and the angle between the aromatic ring planes ( $\alpha$ ) for paracyclophanes are presented in Table 1.

### Substituted [2.2]paracyclophanes

The optimized geometry of [2.2]paracyclophane indicates a parallel structure with a very short interplanar distance of 3.153 Å, much shorter than the sum of van der Waals radii which, for the carbon atom, is 3.4 Å. The introduction of a substituent into the benzene ring of the cyclophane leads to small changes of the interplanar distance ( $d$ ), ring displacement ( $a$ ), and the angle between the ring planes ( $\alpha$ ). This indicates the presence of a strained, close-to-parallel structure of [2.2]cyclophanes and suggests a strong repulsion between the  $\pi$ -electrons of both aromatic rings. The energy of aromatic interaction (AIE) [12] has been computed as the difference between the energy of cyclophane molecules where the bridges were removed and substituted by the H atom of exactly the same geometry. The AIE value reveals a strong repulsion interaction between the benzene rings in [2.2]paracyclophane. The value of AIE for [2.2]paracyclophane is +12.863 kcal/mol, close to that determined by Grimme (14.3 kcal/mol) [12]. The positive AIE values obtained for the majority of the analyzed substituted cyclophanes, with the exception of 1',4-bis(dimethylamino)-1,4'-dinitro[2.2]paracyclophane, show the dominance of the repulsive interactions between the aromatic rings. The AIE values indicate that the introduction of substituents to the

**Scheme 1** Atom numbering for the investigated cyclophanes.  $d$  Distance between the ring planes,  $a$  ring displacement; the planes marked in gray are considered to represent the angle between the ring planes ( $\alpha$ )



**Table 1** Geometrical parameters for cyclophanes according to Scheme 1

	[2.2]Cyclophane			[2.2]Cyclophane-1,9-diene			[3.3]Cyclophane		
	<i>d</i> [Å]	<i>a</i> [Å]	$\alpha$ [°]	<i>d</i> [Å]	<i>a</i> [Å]	$\alpha$ [°]	<i>d</i> [Å]	<i>a</i> [Å]	$\alpha$ [°]
Cyclophane	3.1527	0.0435	0.000	3.1660	0.0000	0.001	3.3055	0.1060	2.586
1-Nitro	3.1238	0.0353	0.851	3.1492	0.0905	1.500	3.3055	0.1060	2.586
1-Dimethylamino	3.1271	0.1522	0.433	3.4255	0.5583	10.632	3.3372	0.1734	0.760
1'-Dimethylamino	3.1607	0.4186	5.238	3.2047	0.1410	5.162	3.4303	0.3529	11.700
1-Dimethylamino-2-nitro	3.1549	0.1005	5.296	3.1505	0.0561	0.009	3.3465	0.5934	0.651
3'-Dimethylamino-4'-nitro	3.1426	0.1525	0.802	3.1281	0.4291	0.359	3.2459	0.7347	2.190
1,2-Dimethylamino	3.1489	0.1177	2.745	3.1111	0.5446	0.790	3.1805	0.9862	7.241
3',4'-Nitro	3.1312	0.0936	1.2070	3.1600	0.1509	2.393	3.2994	0.4714	3.342
1'-Nitro	3.1445	0.1484	1.4070	3.1454	0.1738	0.003	3.3266	0.3236	4.032
1-Dimethylamino-4'-nitro	3.1473	0.1739	5.5240	3.1427	0.0793	0.535	3.3320	0.1125	4.891
4'-Nitro	3.1373	0.0937	1.1270	3.1352	0.2443	1.453	3.3128	0.5473	6.272
1'-Nitro	3.162	0.3911	3.1500	3.1978	0.1842	1.847	3.3388	0.2798	3.448
1-Dimethylamino-4-nitro									
1'-Dimethylamino-4'-nitro									

aromatic rings leads to a decrease in the repulsive character of the interaction between the aromatic rings, independently of the electron-donating or electron-withdrawing properties of the substituent. The unexpected negative AIE values observed for cyclophane, where two  $\text{N}(\text{CH}_3)_2$  substituents in one ring are situated over two  $\text{NO}_2$  substituents in another ring, may be explained by the possibility of some local interactions between the substituents. The steric strain energy (SE) has been calculated following Grimme and Mück-Lichtenfeld [12] and Bachrach [19], employing the homodesmotic reaction (Table 2). For [2.2]paracyclophane, this value is 44.01 kcal/mol and increases after the substituent introduction.

### [2.2]Paracyclophane-7,9-diene

Geometric parameters for [2.2]paracyclophane-1,9-diene are given in Table 1. Contrary to expectation, introduction of the double bond to the bridge does not cause shortening of the inter-ring distance compared to those found for [2.2]paracyclophane. Similarly, the ring displacement between the aromatic rings and the angle between them are close to the parameters for [2.2]paracyclophane. The AIE value indicates the strong strain structure and dominance of steric repulsion in the through-space interaction. The AIE of 13.434 kcal/mol is slightly larger than for [2.2]paracyclophane and

decreases with the introduction of the substituents. Only for the derivative with 1',4'-bis(dimethylamino)-1,4'-dinitro-substituent does the negative AIE value of  $-4.419$  kcal/mol indicates a dominance of attractive interactions. The strain energy (SE) for [2.2]paracyclophane-7,9-diene shows the less strained structure compared to [2.2]paracyclophane. This fact indicates an important contribution of steric repulsion caused by the eclipsing interactions between the  $\text{CH}_2$  groups in [2.2]paracyclophanes.

### Substituted [3.3]paracyclophanes

The geometric parameters for [3.3]paracyclophanes show that the elongation of aliphatic bridges causes an important increase in the inter-ring distance in comparison with [2.2]paracyclophane. The interplanar shift (*d*) and interplane ( $\alpha$ ) angle indicate the parallel-displaced structure with a small angle between the aromatic planes. An increase in the interplanar distance from 3.15 Å for [2.2]paracyclophane to 3.31 Å for [3.3]paracyclophane reduction leads to a decrease in the AIE from 12.86 to 3.153 kcal/mol. For substituted [3.3]paracyclophanes, the negative AIE values, indicating the dominance of the attractive interactions, increase with the number of substituents. An increase in the inter-ring distance in comparison with [2.2]cyclophanes results in a decrease in the destabilizing Pauli repulsion energy. The values of the

**Table 2** Aromatic interaction and steric energies for investigated cyclophanes

	[2.2]Cyclophane		[2.2]Cyclophane-1.9-diene		[3.3]Cyclophane	
	AIE [kcal/mol]	SE [kcal/mol]	AIE [kcal/mol]	SE [kcal/mol]	AIE [kcal/mol]	SE [kcal/mol]
Cyclophane	12.86	44.01	13.43	53.09	3.29	9.84
1-Nitro	11.09	52.20	13.33	47.85	−1.07	6.96
1-Dimethylamino	11.98	55.50	3.32	124.73	−0.19	7.95
1-Dimethylamino	−2.72	73.15	10.61	47.40	−0.23	9.52
1'-Dimethylamino						
1-Dimethylamino	8.98	73.15	9.35	79.55	−1.62	6.13
4'-Dimethylamino						
1-Dimethylamino-2-nitro	4.22	77.44	8.64	43.53	−4.78	4.54
3'-Dimethylamino-4'-nitro						
1,2-Dimethylamino	5.58	80.63	5.71	42.05	−5.38	4.61
3',4'-Nitro						
1-Nitro	11.19	64.67	14.67	46.77	−1.78	8.34
1'-Nitro						
1-Nitro-4-dimethylamino	−2.89	66.72	−4.42	24.89	−11.05	−9.00
1'-Dimethylamino-4'-nitro						
1-Dimethylamino	8.65	69.48	10.75	43.35	−3.03	5.53
4'-Nitro						
1-Dimethylamino	6.97	63.71	5.91	40.66	−3.94	5.83
1'-Nitro						
1-Dimethylamino-4-nitro	5.31	73.75	9.05	37.85	−5.32	7.33
1'-Dimethylamino-4'-nitro						

strain energy (SE) indicate the smallest steric strain in this series of cyclophanes under study.

#### Discussion of the NO<sub>2</sub> and NMe<sub>2</sub> substituent effect on AIE and SE energy for [2.2]cyclophanes, [2.2]cyclophane-1.9-dienes, and [3.3]cyclophanes

Comparison of the AIE and SE values for substituted [2.2] paracyclophane, [2.2]paracyclophane-7,9-diene, and [3.3] paracyclophane shows that the introduction of both electron donor NMe<sub>2</sub> and electron acceptor NO<sub>2</sub> groups increases the attractive interaction between the aromatic rings. This result shows that the substituent effect in paracyclophanes is predominated by the electrostatic interactions.

In [2.2] paracyclophanes, the repulsive interaction between the aromatic rings prevails on the attractive one and decreases the positive values of AIE. The very short interring distances in these compounds mean that the  $\pi$ -orbitals of the different rings may be overlapped. The destabilizing interaction between the occupied orbitals (Pauli repulsion energy) seems to be mainly responsible for positive AIE values. As was shown by Grimme [11], in [2.2]paracyclophane, the LUMO orbital has a considerable bonding character that leads to decreasing Pauli repulsion and attractive “overlap-dispersive” interaction.

The steric strain and the aromatic interaction energy increases with a growing number of substituents. The lack of correlation between the SE and AIE for substituted [2.2] paracyclophanes is the result of the contribution of the strain energy of the alkyl bridges.

Correlation of the SE values with the hardness parameter ( $\eta$ ) [ $\eta = E_{\text{LUMO}} - E_{\text{HOMO}}$ ] [38] (Fig. S1) shows that the strain energy destabilizes the cyclophane molecule.

The results obtained for paracyclophanes show that the attractive intra-space interactions between the aromatic rings increase with the number of substituents, independently of their electronic character. Watt et al. [25] observed a similar effect for benzene dimers and found a correlation between the binding energy and the sum of the absolute value of the field/inductive Hammett constant  $\sum |\sigma_m|$  [39]. The authors stated [25] that this parameter contains some information about the substituent's effect on electrostatic and dispersion contribution to the binding energy. Following Watt et al. [25], we have examined the relationships between the AIE values and the sum of absolute values of inductive Hammett parameters  $\sum |\sigma_m|$ . For [2.2]paracyclophane, [2.2]paracyclophane-7,9-diene, where the repulsive interactions are dominant, no relationships are found. For [3.3]paracyclophane (Fig. S3), the tendency of an increase in AIE with increasing  $\sum |\sigma_m|$  [40] (Fig. S2) permits us to suggest that both electrostatic and dispersion effects contribute to the energy of an

interaction between the aromatic rings in [3.3]paracyclophanes. It is to be noted that only a small quantity of data have been available and the presence of direct interaction between substituents in the multi-substituent derivatives influences the AIE values, as has been suggested above. As was shown for benzene dimers [25], an increase in the surface area in multi-substituted benzenes leads to an increase in the contribution of dispersion in the binding energy, but this effect may be compensated by increasing repulsive interaction. The tendency of an increase in the AIE values with the sum of the molar refractivity substituent constant  $\Sigma Mr$  [40] (Fig S3), which characterizes the dispersion/polarizability interaction, confirms the importance of the contribution of the dispersive interaction for the AIE values.

### The multipole-derived charges on the carbon atoms in the aromatic rings of substituted [2.2]paracyclophane, [2.2]paracyclophane-7,9-diene, and [3.3]paracyclophane

The multipole-derived charges on the carbon atoms presented in Table 1 show that an introduction of electron donor  $N(CH_3)_2$  and electron acceptor  $NO_2$  groups to the aromatic ring causes a decrease in the negative charges on the substituted carbon atom in the aromatic ring of all the investigated cyclophanes, and this effect is more significant for the  $N(CH_3)_2$  than for the  $NO_2$  group. Only small changes are observed for unsubstituted carbon atoms in the rings and carbon atoms of the aliphatic bridges in [2.2]paracyclophanes and [3.3]paracyclophane. In [2.2]cyclophane-1,9-diene, the multipole-derived charge on 5,5' C atoms and atoms of the bridges are sensitive to the substituent effects. A similar effect is observed in mono- and multi-substituted cyclophane derivatives. The observation that the substituents lead to a decrease in the negative charge on the carbon atom of aromatic rings connected with the substituent, independently of their electron-withdrawing or electron-donating character, confirms the local, electrostatic origin of the substituent effect for the investigated paracyclophanes.

### QTAIM analysis of substituted [2.2]paracyclophane, [2.2]paracyclophane-7,9-diene, and [3.3]paracyclophane

In order to obtain information concerning the presence of the through-space orbital interactions between the C atoms of the aromatic rings, we have performed the Quantum Theory Atom In Molecule (AIM, QTAIM) analysis [41–43]. The QTAIM analysis is a very efficient tool in the investigation of closed-shell interactions, like conventional hydrogen bonds,  $H\cdots H$  interactions, and various weakly bonded complexes [42–47]. The presence of the bond path between the given atoms with the electron density at the bond-critical point

(BCP)  $\rho(r) < 0.1$  a.u. and positive Laplacian of the electron density are typical for closed-shell interactions. The small ellipticity of electron density ( $\epsilon$ ) at the BCP and linearity of the bond are an indication of the stable interaction [48].

The QTAIM analysis has been previously applied in the studies of [2.2]paracyclophane [10, 11], [2.2]metacyclophane [9], and [n,n]paracyclophane complexes with cations [13]. In the previous paper [21], we applied the QTAIM analysis to investigate the through-space interactions in a series of unsubstituted and substituted [2.2]paracyclophanes. The presence of a  $C\cdots C$  bond path between the C atoms belonging to different rings in the [2.2]paracyclophane molecule and the charge density at the BCP  $\rho(r) > 0.0125$  a.u. were taken as evidence for the presence of through-space orbital interactions between the C atoms [21]. For [2.2] paracyclophane and [2.2]paracyclophane-7,9-diene and their derivatives investigated in this work, no bond path between the  $C\cdots C$  atoms in the different rings has been detected. For [3.3]paracyclophane, two bond paths with the  $\rho(r)$  of 0.0076 a.u. have been observed, which suggests the existence of a weak orbital interaction of the C atoms in different rings. As can be seen, the decreased strong repulsion interaction between the aromatic rings by increasing through-bond distance permits the appearance of very weak orbital interactions.

For the three groups of substituted paracyclophanes investigated in this work, the bond paths with the  $\rho(r)$  values from 0.0076 to 0.0083 a.u. have been observed, but only some of them are indicators of the presence of a stable orbital interaction between the C atoms in different rings. No influence of the substituents on the charge density at the BCP, and hence the energy of the  $C\cdots C$  interaction, has been observed. QTAIM analysis evidences the existence of numerous non-covalent interactions between the substituents. The interactions between the O atom of the  $NO_2$  group and the H atom of the  $N(CH_3)_2$  group, present in the same or different ring in a vicinal position and situated one above another in different rings, have been observed. These interactions may be assigned to the  $CH\cdots O$  hydrogen bond. Also the  $O\cdots H$  interactions between the nitro group and the H atom of the aromatic ring as well as the  $H\cdots H$  interactions between the H atoms of the methyl group and H atoms of the bridges and the aromatic rings are shown. The  $CH\cdots O$  hydrogen bonds between the nitro and dimethylamino group in different rings are worth noticing, particularly for fourthly substituted cyclophanes with 1',4-bis(dimethylamino) and 1,4'-dinitro groups. For 1',4-bis(dimethylamino)-1,4'-dinitro [2.2]paracyclophane, an  $H\cdots O$  bond path with  $\rho(r)$  of 0.0052 a.u. has been observed. For the [3.3]paracyclophane analog of this compound, two  $H\cdots O$  bond paths with a  $\rho(r)$  value of 0.0114 and 0.0086 a.u. and one  $N\cdots O$  bond path (with  $\epsilon > 1$ ) have been found. For the same derivative of [2.2] paracyclophane-7,9-diene, the  $H\cdots O$  bond paths with  $\rho(r)$

equal to 0.0113, 0.0071, and 0.0071 a.u. and two N...N bond paths (with  $\epsilon > 1$ ) have been shown. The presence of the stable CH...O interactions between the substituents in the different rings, apart from the through-space stacking interactions between the aromatic rings, contributes to the total AIE value. This may explain the exceptional negative AIE values:  $-2.893$ ,  $-4.419$ , and  $-11.054$  kcal/mol for [2.2]paracyclophane and [2.2]paracyclophan-7,9-diene, and [3.3]paracyclophane, respectively. The above results have shown that in the substituted paracyclophanes the AIE value is not only a measure of the through-bond interaction between the aromatic rings, but has some contribution resulting from the direct through-space interaction between the substituents, which explains the scattering of the points in the AIE versus  $|\Sigma\sigma_m|$  plot (Fig S2).

We have applied the QTAIM analysis to answer the question of whether the atoms of the bridges joining the aromatic rings can participate in the interactions with the rest of the molecule. The QTAIM plots for the structures in which the bridges linking the aromatic rings have been replaced by the H atoms show that interactions in those molecules are different. The most significant difference in the QTAIM plots of the cyclophanes and their analogs in which the CH=CH and CH<sub>2</sub>CH<sub>2</sub> bridges have been replaced by the H atoms is the appearance of new bond paths joining the H atoms added in different rings. At the same time, the bond paths joining the atoms of the substituents with the H atoms of the bridges have disappeared. The values of  $\rho(r)$  for the through-space C...C interaction remain the same, but the increasing ellipticity of the electron density at BCP and nonlinearity of the C...C bond path suggests an increase in instability of these interactions. The results show that a removal of the cyclophane bridges causes some changes in the very weak orbital interactions between the aromatic rings.

### NCI analysis of substituted [2.2]paracyclophane, [2.2]paracyclophane-1,9-diene, and [3.3]paracyclophane

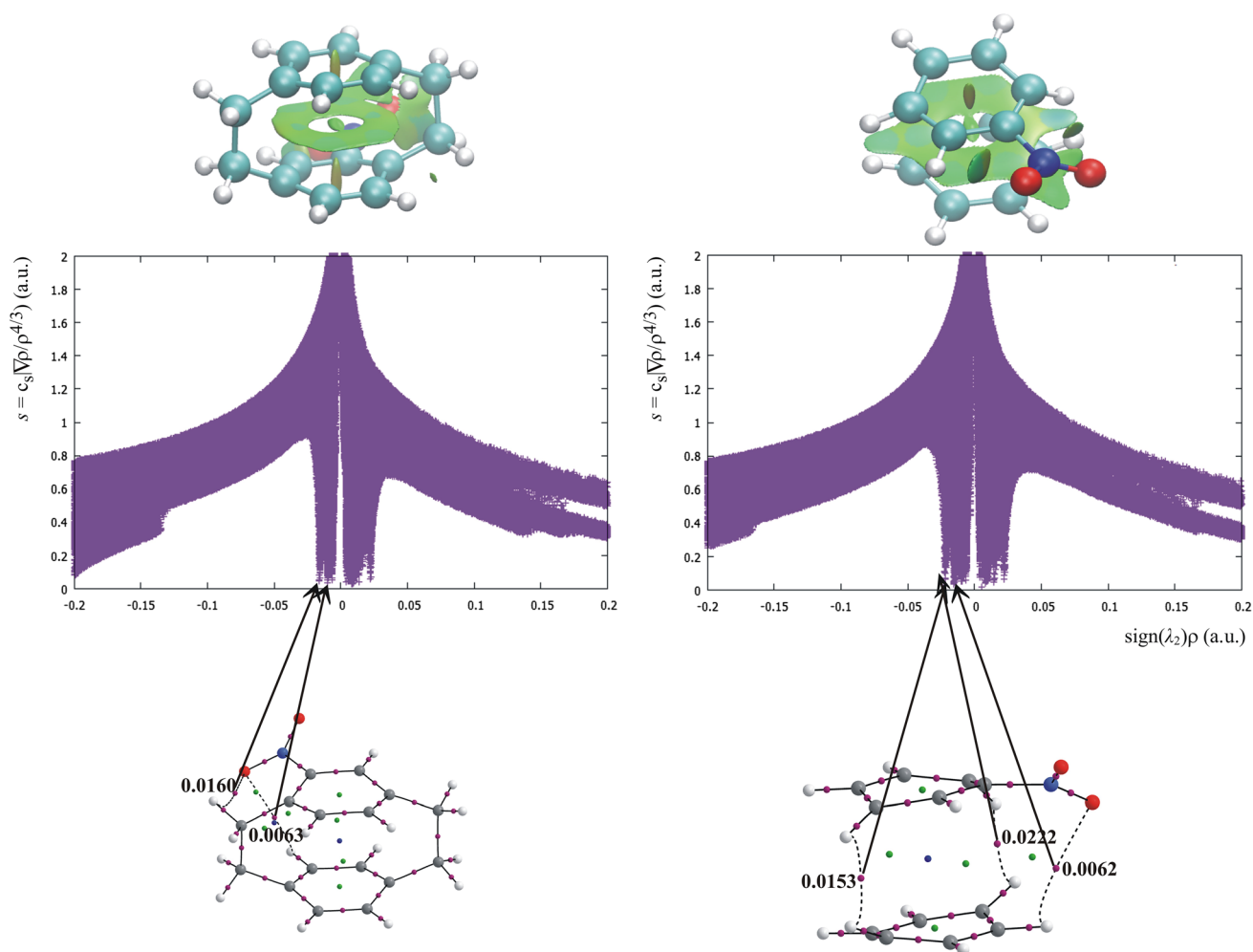
To obtain information concerning the dispersive interactions in investigated cyclophanes, the non-covalent interaction (NCI) approach has been applied [17, 49]. This method, which is an efficient tool to analyze and visualize weak non-covalent interactions, is based on the plot of the reduced density gradient versus the electron density multiplied by the sign of the second Hessian eigenvalue ( $\lambda_2$ ). Multiplication of electron density by the sign of the second Hessian eigenvalue differentiates the repulsive ( $\text{sign}\lambda_2\rho(r) > 0$ ) and attractive ( $\text{sign}\lambda_2\rho(r) < 0$ ) interactions. Typical dispersion interactions usually appear as spikes at very low density values ( $\rho(r) < 0.01$  a.u.), whereas stronger interactions, as hydrogen bonds, appear at higher density values ( $0.01 < \rho(r) < 0.05$  a.u.) of the NCI plot [46, 47]. The second

possibility of presentation of the non-covalent interactions in the frame of the NCI method is the visualization of electron-density-gradient isosurfaces in real space for the molecule and typical colors present a particular type of interaction: blue for attractive, red for repulsive, and green for intermediate interaction. NCI analysis for [2.2]paracyclophanes was performed previously [21].

The NCI analysis for the investigated cyclophanes evidenced the existence of numerous attractive and repulsive weak non-bonding interactions, presented by positive and negative  $\rho(r)$  values for the spikes in the NCI plot. For all cyclophanes, repulsive interactions dominate over the attractive ones. For substituted, and particularly for the multi-substituted paracyclophanes, the number of spikes corresponding to both attractive and the repulsive interaction increases. The non-bonding interactions have been visualized by green gradient surfaces. The gradient surface shows that the weak non-bonding interactions are present not only between the aromatic rings, but also between some of the substituents in a vicinal position or closely situated in both the rings and also between the substituents in the bridges and the aromatic rings (Fig. 1).

## Conclusions

1. The aromatic interaction energy (AIE) as well as the steric energy (SE) for the investigated cyclophanes is influenced by the structure and length of the bridges joining the aromatic rings. For [2.2] paracyclophanes, the positive AIE values indicate the dominance of repulsive interactions, while for substituted [3.3]paracyclophanes, the negative AIE values indicate the dominance of attractive interaction.
2. The AIE values for paracyclophanes under study show that the introduction of substituents into the benzene rings, independently of their electronic character, increases the attractive interaction between the aromatic rings. This result shows that the electrostatic interactions play a dominant role in the substituent effect on the attractive through-space interaction in paracyclophanes.
3. An analysis of the multipole-derived charges on the carbon atoms in aromatic rings of paracyclophanes under study suggests that the substituents' effect on through-space interactions between the aromatic rings is controlled by local, electrostatic interactions.
4. The QTAIM analysis evidences the existence of the weak orbital through-space C...C interaction between different rings for [3.3]paracyclophane and in some substituted derivatives. For substituted [2.2] and [3.3]paracyclophanes, the presence of numerous non-covalent interactions between the atoms of the NO<sub>2</sub> and NMe<sub>2</sub>



**Fig. 1** NCI surface and NCI plot for 1-nitro[2.2]paracyclophane (left) and its analog without the aliphatic bridges (right) compared with the AIM diagram

groups and the H atoms of the aliphatic bridges and aromatic ring was stated.

- Formation of the through-space  $\text{CH}\cdots\text{O}$  hydrogen bonds between  $\text{NO}_2$  and protons from the  $\text{N}(\text{CH}_3)_2$  group or other aliphatic or aromatic protons stabilizes the stacking interaction between the aromatic rings in the paracyclophanes under study.
- The NCI plots for the investigated compounds evidence the presence of dispersive and other non-bonding attractive and repulsive interactions between the aromatic rings. The gradient surfaces confirmed the existence of weak interactions between the aromatic rings and the substituents. The comparison of the gradient surface for the structure where the bridges are replaced by the H atoms with the parent compound shows differences in the non-covalent interactions.

**Acknowledgements** The Wrocław Center for Networking and Supercomputing is acknowledged for generous allocations of computer time. This work is supported by Wrocław Medical University Grant No. ST.D050.18.003.

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