Introduction

The [4+2] Diels–Alder cycloaddition of benzene is either exceptionally slow or forbidden owing to its aromatic nature.\(^{[1,2]}\) Harsh reaction conditions, Lewis-acidic catalysts such as AlCl\(_3\), or highly reactive dienophiles such as dicyanoacetylene, perfluoro-2-butyne, or tetrafluorobenzene are required to enable reactions with benzene (Scheme 1a).\(^{[1,2]}\) In contrast, the strained arene-like paracyclophanes exhibit an remarkable enhancement of reactivity (see Scheme 1b).\(^{[2]}\) This enhanced reactivity of cyclophanes was originally proposed to arise from the localized cyclohexatriene nature of the \(\pi\)-conjugated core.\(^{[3]}\) Sola and co-workers found a decrease in aromaticity in bent benzene rings compared to planar benzene by evaluating the NICS parameter.\(^{[4]}\) Later, the enhanced reactivity was ascribed primarily to the concomitant release of strain in the transition state (TS).\(^{[5]}\) A revealing example of the difference in reactivity between benzene and [5]metacyclophane\(^{[6]}\) is the transfer of the carbene-like phosphinidene P(\(\text{Ph})\)\(_4\) from a phosphinorbornadiene to the strained hydrocarbon by [4+1] cycloaddition (Scheme 1c).\(^{[7]}\) Removal of the transition metal group reduces the stability of the product, which then undergoes a cheletropic elimination to regenerate [5]metacyclophane.\(^{[8]}\) Early semi-empirical MNDO and \(\text{X}\alpha\) calculations attributed the reduced HOMO–LUMO (H–L) gap in cyclophanes to the
distortion of the $\pi$ framework.\textsuperscript{[9]} A recent high-level DFT analysis by Fernández and co-workers on (2,7)pyreneophanes identified reduced activation strain as the main reason for its enhanced Diels–Alder cycloaddition reactivity over that of the parent planar pyrene molecule,\textsuperscript{[10]} whereas both the diminished strain in the product and the increased interaction of HOMO–1 of the arene with the LUMO of the phosphinidine were considered to be the main factors for the [4+1] cycloaddition to [5]metacyclophane.\textsuperscript{[7]} Very recently, orbital interactions, and not activation strain, were proposed as the primary channel controlling the reactivity of Diels–Alder cycloadditions with strained cycloalkenes.\textsuperscript{[11]} Moreover, UV/Vis measurements on $n$paracyclophanes indicated redshifted absorption maxima upon decrease in bridge length, which was ascribed to the decrease of the H–L gap.\textsuperscript{[12]} This suggests that modulating the H–L gap of the arene by structural distortion influences its reactivity. Hence, a mechanism other than predistortion may govern the reactivity for Diels–Alder cycloaddition with benzene molecules. To confirm this hypothesis and to determine the factors controlling the Diels–Alder reactivity of cyclophanes, we undertook a comprehensive quantum-chemical study of the Diels–Alder cycloaddition of benzene (B) and its strained analogues [5]paracyclophane (P)\textsuperscript{[13]} and [5]metacyclophane (M)\textsuperscript{[14]} with acetylene (A). Acetylene was chosen as the dienophile in the investigated Diels–Alder reactions for the sake of simplicity, as it is the archetypal dienophile reactant. In line with expectation, the activation barrier for the reactions with the dicyano-substituted acetylene is about 10 kcal mol\textsuperscript{−1} less than for the parent acetylene and trends in reactivity are the same (Table S1 in the Supporting Information).

### Theoretical Methods

#### Computational details

Kohn–Sham DFT calculations were performed with the ADF,2017.208 program.\textsuperscript{[14]} The GGA density functional BLYP\textsuperscript{[15]} with finite damping introduced by Becke and Johnson (BJ), BLYP-D3(BJ),\textsuperscript{[14]} was used for the geometry optimizations of all stationary states as well as for the reaction coordinate by using the activation strain model (ASM)\textsuperscript{[16]} and energy decomposition analysis (EDA).\textsuperscript{[17]} As demonstrated by Grimme et al., BJ damping shows improvement over DFT-D3 in calculating barrier heights and reaction energies.\textsuperscript{[18]} Specifically, BJ damping outperforms other DFT functionals in terms of more accurate treatment of the noncovalent and $\pi$–$\pi$ interactions leading to both more accurate cyclophane geometries and more accurate reaction barrier heights.\textsuperscript{[16,19]} All calculations were performed with the all-electron TZ2P basis set, which is of triple-$\zeta$ quality, combined with two sets of polarization functions for all the atoms.\textsuperscript{[20]} The accuracy of the integration grid (Becke grid)\textsuperscript{[21]} and fit scheme (Zim fit)\textsuperscript{[22]} were set to VERY-GOOD. The energies reported herein are all for isolated molecules. Analytical frequency\textsuperscript{[23]} calculations were performed to characterize the nature of the stationary points. The reactants and the cycloadducts showed real frequencies indicating their location on the potential-energy surface (PES) as local minima, while the transition state (TS) showed one imaginary frequency. The character of the eigenvector corresponding to the imaginary frequency was analyzed to ensure it was associated with the reaction under consideration. The PES of the reaction was obtained by performing intrinsic reaction coordinate (IRC) calculations.\textsuperscript{[24]} All of the reported energies are electronic energies without zero-point energy correction. Furthermore, the computed reactivity trends are unchanged on considering either the Gibbs free or electronic energies (Table S8 in the Supporting Information).

#### Activation strain model

The activation strain model (ASM), also known as the distortion/intersection model,\textsuperscript{[25]} is a fragment-based approach that essentially describes the height of the reaction barrier in terms of the reagents involved along the reaction coordinate $\zeta$.\textsuperscript{[26]} This approach has been paramount for the current understanding of different fundamental transformations in organic and organometallic chemistry.\textsuperscript{[26]} In this model, the PES $\Delta E(\zeta)$ is decomposed along $\zeta$ into two energy components: the strain $\Delta E_{\text{strain}}(\zeta)$ associated with deforming the reactants from their equilibrium structures and the interaction $\Delta E_{\text{int}}(\zeta)$ between these distorted reactants along $\zeta$. The activation barrier arises due to an intricate interplay between $\Delta E_{\text{strain}}(\zeta)$ and $\Delta E_{\text{int}}(\zeta)$ [Eq. (1)].

$$\Delta E(\zeta) = \Delta E_{\text{strain}}(\zeta) + \Delta E_{\text{int}}(\zeta)$$ \hspace{1cm} (1)

#### Energy decomposition analysis

$\Delta E_{\text{int}}(\zeta)$ was further analyzed in terms of quantitative molecular orbital theory as contained in Kohn–Sham DFT in combination with a canonical EDA.\textsuperscript{[18]} The EDA decomposes $\Delta E_{\text{int}}(\zeta)$ into the following physically meaningful energy terms [Eq. (2)]:

$$\Delta E_{\text{int}}(\zeta) = \Delta V_{\text{distal}}(\zeta) + \Delta E_{\text{Pauli}}(\zeta) + \Delta E_{\text{disp}}(\zeta)$$ \hspace{1cm} (2)

Therein, $\Delta V_{\text{distal}}(\zeta)$ represents the quasiclassical electrostatic interactions between the unperturbed charge distributions of the distorted reactants. The Pauli repulsion $\Delta E_{\text{Pauli}}(\zeta)$ emerges due to repulsive exchange interactions between the occupied closed-shell orbitals. The orbital interactions $\Delta E_{\text{disp}}(\zeta)$ comprise stabilizing interactions such as electron-pair bonding, charge transfer between occupied and unoccupied molecular orbitals, and polarization (empty–occupied orbital mixing on one fragment due to the presence of another fragment). Lastly, $\Delta E_{\text{disp}}(\zeta)$ accounts for the dispersion forces originating from noncovalent interactions or weak interactions.

#### Results and Discussion

The optimized geometries of the ground-state reactants are shown in Figure 1. The cyclophanes are formed by the addition of a short five-membered oligomethylene bridge to benzene (B) at the para and meta positions. The oligomethylene bridge induces several geometrical distortions in the cyclophanes. The most prominent is the out-of-plane bending of the aromatic core ($\alpha$ and $\gamma$) into a symmetrical [5]paracyclophane (P) and an
asymmetrical [5]metacyclophane (M) boat-like configurations (Figure 1a). Additionally, there is distortion in the benzylic carbon–carbon bonds of the bridge relative to the aromatic core, depicted as β.

We began by analyzing the Diels–Alder reactivity of B, P, and M with A. The reactions of B and P proceed via concerted synchronous transition states, whereas that of M is concerted asynchronous (Figure 2). The Diels–Alder cycloaddition reactions of the cyclophanes proceed earlier compared to benzene. The late transition state in B is associated with the highest activation energy (37.2 kcal mol⁻¹), while the earlier TSs for cyclophanes P (23.6 kcal mol⁻¹) and M (16.7 kcal mol⁻¹) are associated with markedly lower barriers, which is consistent with the Hammond–Leffler postulate.²⁸ The activation energy is reduced by up to about 20 kcal mol⁻¹ and the total reaction energy \( \Delta E_{\text{rxn}} \) changes from being endothermic (6.9 kcal mol⁻¹) to highly exothermic (ca. −28 kcal mol⁻¹) when moving from B to the cyclophanes.

The physical factors governing the reactivity of B, P, and M toward A were analyzed quantitatively by means of ASM and EDA and are represented graphically in Figure 3. Figure 3b reveals that the enhanced Diels–Alder cycloaddition reactivity for M results from a significant decrease in strain energy \( \Delta E_{\text{strain}} \) whereas \( \Delta E_{\text{rel}} \) is comparable to B. Decomposing \( \Delta E_{\text{strain}} \) into the strain-energy components of the two reactants (M and A) \( \Delta E_{\text{strain(diene)}} \) and \( \Delta E_{\text{strain(dienophile)}} \) reveals that the much lower strain originates largely from the reduced strain contribution of M (Figure 3c). The reason for this behavior is that the cyclophane bridge connecting the meta positions (i.e., C1 and C3, see Figure 1a for atom numbering) pulls the two sides of the aromatic core (i.e., C1–C6 and C3–C4) towards each other. As a consequence, the bond-forming carbon centers C2 and C5 are forced out of the aromatic plane into a boat conformation and thereby facilitate formation of new C–C bonds with the incoming A. Hence, the equilibrium geometry of M resembles more the TS geometry than that of B, which is not subject to such predistortion. The aromatic core of P is, of course, also predistorted, but unlike that of M not with respect to the bond-forming carbon centers (i.e., C1 and C4), resulting in a \( \Delta E_{\text{strain}} \) similar to that of B.

To quantify the contribution of strain towards the Diels–Alder barrier heights of B, P, and M, we analyzed the energy terms at a consistent TS-like geometry, because the magnitude of the strain and the interaction energy terms is highly dependent on the position of the TS on the reaction coordinate.¹⁶,²⁷ Therefore, to ensure an equitable comparison of energies, we analyzed the geometries in which the shorter of the two C–C bond-forming lengths is 2.15 Å. Hereafter, this position on the

**Figure 1.** a) Illustration with atom numbering, where red bold numbers indicate the bond-forming C atoms that react with acetylene, and structural parameters: out-of-plane bending of the aromatic core (α and γ) and bending of the bridge with respect to the core (β). The C=C double bonds in the aromatic core of P and M have been omitted for clarity. b) Ground-state equilibrium geometries of the dienes, computed at the BLYP-D3(BJ)/TZ2P level of theory.

**Figure 2.** Transition state structures with forming bond lengths [Å], computed activation energy barrier \( \Delta E^* \) [kcal mol⁻¹] (blue), relative rate constants \( \text{k}_{\text{rel}} \) (black), and total reaction energies \( \Delta E_{\text{rxn}} \) [kcal mol⁻¹] (red) for the Diels–Alder cycloaddition reactions of B, P, and M with A, computed at the BLYP-D3(BJ)/TZ2P level of theory.
reaction coordinate is denoted as $z^*$ and the corresponding energy terms as $D_{E^*}$. The structures and energies at $z^*$ are similar to the actual TSs and the trend in energies mirrors the trend at the real TS (see Figure 2 and Table 1).

Smaller changes in $\alpha$ and $\gamma$ over the course of the Diels–Alder reaction result in less-destabilizing $D_{E^*_\text{strain(diene)}}$. Figure 4 shows that in order to react with $A$, $M$ must be distorted least from its equilibrium geometry ($\Delta\alpha = 17^\circ$ and $\Delta\gamma = 19^\circ$), then $P$ ($\Delta\alpha = \Delta\gamma = 22^\circ$), and then finally $B$ ($\Delta\alpha = \Delta\gamma = 31^\circ$). Therefore, at $z^*$, the $D_{E^*_\text{strain(diene)}}$ value of $M$ is 14.1 kcal mol$^{-1}$, which is about 11.6 kcal mol$^{-1}$ lower than those of both $B$ and $P$ (see Table 1). As already noted, the geometry of $M$ shows the smallest change due to its favorable predistortion. The substantially lower $D_{E^*_\text{strain}}$ of $M$ compared to $B$ and $P$ also originates from the lower $D_{E^*_\text{strain(diene)}}$ at $z^*$ (Table 1). This effect was traced to the relatively small distortion of $A$ in the Diels–Alder cycloaddition, which is related to the asynchronous nature of its TS. The asynchronicity stems from the interaction of the two nonidentical (different local environments) carbon atoms C2 and C5 in $M$, which causes the new C–C bonds to form at different rates. This behavior is evident from the different C2-C1-H and C1-C2-H bond angles of $A$ in the $z^*$ of $M$–$A$ (see Figure 4a for atom numbering) of 153 and 160$^\circ$, respectively. These distortions are, however, much larger ($\sim 150^\circ$) for $B$–$A$ and $P$–$A$ compared to the linear acetylene equilibrium geometry. Previously, it was concluded that concomitant release of strain in the diene drives the Diels–Alder cycloaddition reaction of $M$, but instead it appears that its enhanced reactivity results from a reduced buildup of strain along the reaction coordinate in both the diene and dienophile.

The enhanced reactivity of para-bridged $P$ compared to $B$ originates from the difference in their stabilizing $D_{E_{\text{int}}}$ component (Figure 3b). EDA analysis shows that this arises mainly from the different contributions of the orbital interaction term ($\Delta D_E = 9$ kcal mol$^{-1}$; Figure 3d; Table S2 in the Supporting Information). A comprehensive Kohn–Sham molecular orbital (KS-MO) analysis revealed that the more stabilizing $D_{E_{\text{int}}}$ for $P$ arises primarily from a stronger inverse electron-demand interaction from HOMO$_A$ to LUMO$_P$ (Figure 5). The P–A donor–ac-
The receptor orbital-energy gap of 4.4 eV and bond overlap of 0.24 are more favorable for P than for B (orbital-energy gap = 4.9 eV, S = 0.23). Importantly, both normal and inverse orbital interactions are more stabilizing for P than for B due to smaller orbital-energy gaps, but the former contributes to a lesser degree due to poor HOMO$_P$/HOMO$_A$ bond overlap (both orbitals participate in a normal electron-demand interaction) with LUMO$_A$. The poor overlap results from a small amplitude of the occupied frontier orbitals at the bond-forming carbon centers (see Figure 5). Thus, both normal and inverse electron-demand orbital interaction in P–A is driven by the decrease in orbital-energy gaps.

Of the three Diels–Alder cycloadditions, the orbital-energy gap is the smallest and thus most favorable along the P–A reaction coordinate (Figure 6). The origin of this behavior is the smaller H–L gap within the diene P (3.2 eV at its equilibrium geometry) compared to that within B (5.0 eV at its equilibrium geometry). Such a small H–L gap is caused by structural distortion imparted by the short para bridge, which manifests itself in a large out-of-plane bending of the aromatic core ($\alpha \approx 23^\circ$).
and the related bending of the bridge ($\beta \approx 30^\circ$) at the equilibrium geometry. To understand how these geometrical distortions contribute to a markedly lower H–L gap, we performed a comprehensive quantitative KS-MO analysis.

Out-of-plane distortion $\alpha$ of the planar aromatic core causes the destabilization and stabilization of $\pi$-HOMO and $\pi^*$-LUMO, respectively (Figure 7a and Figure S2 in the Supporting Information). The antibonding $\pi$-HOMO is destabilized due to an increase in $\pi-\pi$ overlap $S_{\pi-\pi}$ between the $p_{\pi}$ amplitudes of the

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**Figure 6.** Orbital-energy gap analysis along the reaction coordinate (black: B–A, red: P–A, blue: M–A), computed at the BLYP-D3(BJ)/TZ2P level of theory. Diamonds represent the position of the TS.

**Figure 7.** a) Schematic $\pi$-fragment-orbital interaction diagram between two equivalent allylic fragments depicting the lowering of H–L gap upon out-of-plane distortion ($\alpha$) relative to flat benzene (in gray). The factors that change the H–L gap are: b) the increase in overlap ($S_{\pi-\pi}$) between allylic $\pi$-HOMOs, c) the electrostatic stabilization of the allylic $\pi^*$-LUMOs ($\psi_A$ and $\psi_B$ denote the $\pi^*$-LUMOs belonging to fragments A and B, respectively), and d) the decrease in overlap ($S_{\pi^*-\pi^*}$) between allylic $\pi^*$-LUMOs with the red dotted lines indicating out-of-phase overlap between the diffuse $p_{\pi}$ orbitals.
π-HOMO fragment orbitals of the equivalent allylic C,H₃ triradical fragments forming the overall benzene molecule (Figure 7b and Table S3 in the Supporting Information). The π*-LUMO is stabilized due to the attractive Coulombic (electrostatic) interaction stemming from the increase in overlap of the π*-LUMO fragment orbital of one allylic C,H₃ triradical fragment with the nuclei of the other and vice versa (Figure 7c).[31] This overlap increases as the spatial proximity between the allylic fragments decreases. As a result, the isolated allylic π*-LUMO is stabilized, which in turn stabilizes the overall bonding π*-LUMO of benzene (see Figure 7a and Figure S2 in the Supporting Information, quantitative details are provided in Table S4 in the Supporting Information). Contrary to intuition, there is a decrease in π*-p overlap (S₀,π* ) upon bending (Table S3 in the Supporting Information). This is caused by the cancellation of overlap on out-of-phase mixing of the diffuse pₓ amplitude of the π* LUMO on the terminal C atom of one fragment and the front C atom of the other (Figure 7d). Thus, the H–L energy gap within B decreases upon out-of-plane distortion by 1) increased π–π overlap that destabilizes the HOMO, and 2) enhanced electrostatic stabilization that stabilizes the LUMO despite an unprecedented reduction in π*–π* overlap. Furthermore, an increase in the bonding of the benzyl C–C bond β (see Figure 1a) results in mixing of the σ and π fragment orbitals of the ring substituents and the aromatic core, respectively, which thereby enhances both the destabilization of the antibonding π-HOMO and the stabilization of the bonding π* LUMO and thus contributes to decreasing the H–L gap even further (Figure 8 and Figure S3 in the Supporting Information). The outlined relationship between structural distortion (geometrical strain) and the H–L gap sheds new light on the findings of Hopf and co-workers, who attributed the enhanced reactivity of n-paraacyclophanes over B solely to the sterically strained geometries.[30]

Thus, structural distortion reduces the H–L energy gap within P and accelerates its Diels–Alder cycloaddition because of the enhanced P–A orbital interaction, as reflected in ∆Eₛₐₚₐₜ (red curves in Figure 6). Cyclophane M exhibits a smaller M–A orbital-energy gap than the parent system B–A at the start of the cycloaddition (blue and black curve, respectively, in Figure 6). However, the orbital-energy gaps become similar around the TS, despite the fact that the H–L gap within M is decreased relative to that within B (4.0 eV in M versus 5.0 eV in B at equilibrium geometry) due to a similar mechanism as discussed for P. Note that although HOMO–1 of M interacts with LUMO₂ in the early stages of the reaction, HOMO and HOMO–1 of M being nearly degenerate (Δɛ = 0.30 eV) invert near the TS due to the change in electronic structure caused by increased out-of-plane distortion along the reaction coordinate (see Figure S4 in the Supporting Information). The reason for the similar orbital-energy gap around the TS comes from a larger H–L energy gap within the dienophile A, as its distortion is much smaller around the TS (Figure 4b) on reacting with M than it is for both B or P. In other words, the initial relatively small M–A orbital-energy gap increases around the TS due to the smaller C–C–H bending of A, which translates into a higher π-HOMO and a lower π*-LUMO energy.[32] The fact that the bonding of A is relatively small is related to the asynchronous nature of the TS in M–A, as already discussed above. The outcome is a larger normal and inverse electron-demand orbital-energy gap and consequently a less stabilizing H–L energy gap and consequently less stabilizing π*-LUMO energy.

Next, we assessed whether, besides structural distortion, the (CH₃)₂ bridge of the cyclophane also exerts an electronic influence on the reactivity, but found the effect on reaction barrier heights to be minimal. For example, removing the bridge from M (M-nb) and P (P-nb) leads to negligible changes in ∆Eₛₐₚₐₜ. Removing the distortion in the aromatic core and simulating the electronic effect of the bridge by using meta- and para-xylene led to activation barrier heights that are almost comparable to that of B. It then appears that predistortion of the aromatic core by the bridge enhances the Diels–Alder cycloaddition reactivity and not the substituent effect itself (see Figure S5 and Table S6 in the Supporting Information).

To apply these insights for the design of aromatic Diels–Alder reactions with significantly lower activation energy barriers, we combined the two modes of activation induced by geometrical distortion: reduced activation strain of the diene connected by a meta bridge and enhanced orbital interactions through a reduced H–L gap within the diene connected by a para bridge. The latter can also be addressed through means other than distortion, such as heteroatom substitution in the aromatic core. Heteroatom-substituted benzene derivatives of main group elements show interesting electronic properties, such as a smaller H–L gap as well as an enhanced cycloaddition reactivity.[33] For example, in contrast to benzene, both substituted phosphabenzene[34] and substituted azadiene[35] have been shown to react with mild dienophiles, albeit sluggishly, indicating a still relatively high activation barrier. Therefore, as proof-of-concept, we systematically designed and explored the behavior of the aromatic Diels–Alder cycloaddition for four heteroatom-functionalized [5]metacyclophanes: The C₄ atom of M is substituted for one heteroatom (see Figure 1a for atom numbering) in Mₚₚ (pyridine core) and Mₚₙₚ (phospha-
benzene core); the C4 and C6 atoms of M are substituted for two heteroatoms in M_{2N}(pyrimidine core) and M_{2P}(diphosphabenzenecore). We envisioned that introducing a heteroatom into the aromatic core of the favorably predistorted [5]metacyclophane would cause a further reduction in the H–L gap within M (see Table S7 in the Supporting Information) and result in an enhanced stabilizing orbital interaction with the dienophile in tandem with a reduced activation strain. Figure 9 summarizes the progressive decrease in activation barrier on successive introduction of strain and/or interaction activation through geometrical distortion and subsequent heteroatom substitution in the aromatic core. As anticipated, the computed activation barriers decrease sharply from single activation, that is, from bending of benzene to the [5]metacyclophane, to two heteroatom into the aromatic core of the favorably predistorted phabenzenecore). We envisioned that introducing a heteroatom into the aromatic core of the favorably predistorted [5]metacyclophane would cause a further reduction in the H–L gap within M (see Table S7 in the Supporting Information) and result in an enhanced stabilizing orbital interaction with the dienophile in tandem with a reduced activation strain. Figure 9.

Figure 9. Combining the modes of activation for aromatic Diels–Alder cycloadditions at the carbon centers starting from the archetypal B. Activation energies $\Delta E^\ddagger$ in black, changes in the activation energy barrier $\Delta \Delta E^\ddagger$ introduced by an additional mode of activation in green, computed at the BLYP-D3(BJ)/TZ2P level of theory. All energies are in kcal mol$^{-1}$. during a cycloaddition has a higher activation barrier than formation of the corresponding C–C bond.[34,90] We observed this expected trend in barrier height for the cycloaddition of M_{N}, which is associated with a much higher activation barrier ($\Delta E^\ddagger = 26.6$ kcal mol$^{-1}$), see Scheme 2) than that of its parent M (see Figure 1a for atom numbering) is formed (see Scheme 2). Formation of a C–N bond metacyclophanes, M_{2N} and M_{2P}, both show enhanced interaction compared to [5]metacyclophane, coming mostly from an increase in orbital interactions in the former and a decrease in Pauli repulsion in the latter, along with a reduced activation strain in both cases (Figures S6 and S7 in the Supporting Information). These factors are fully consistent with the findings of earlier studies.[35c–d] The difference in cycloaddition barrier between the reactive nitrogen- and the relatively less reactive phosphorus-substituted metacyclophanes arises from a higher destabilizing activation strain in the latter compared to the former (Figures S6–S9 in the Supporting Information).

To expand the scope of the work, we also analyzed the Diels–Alder reactivity of heteroatom-substituted metacyclophanes in which one C–C and one C–X bond (X=N, P substituted at the C2 center of M, see Figure 1a for atom numbering) are formed (see Scheme 2). Formation of a C–N bond
of $M^{32}$ and results in the smallest H–L gap within $M_{P}$ of 2.5 eV at equilibrium geometry (see Table S7 in the Supporting Information), compared to the other dienes in our study. Moreover, the orbital overlap of the key orbitals participating in inverse electron-demand interaction, HOMO$_{A}$ and LUMO$_{M(P)}$, is more favorable ($S = 0.30$) compared to $M$ or even $P$ ($S = 0.22$ and 0.24 for $M$ and $P$, respectively). This increase in overlap stems from a large amplitude of the $M_{P} \pi^{*}$-LUMO on the bond-forming phosphorus center due to the low-lying empty $p$ orbital of phosphorus. In this way we rationally tune the aromatic Diels–Alder cycloaddition rate of benzene to cover a wide spectrum of activation barriers through simple manipulation of different activation channels (see Scheme 3).

**Conclusion**

The acceleration of aromatic Diels–Alder reactions through structural distortion of the aromatic core, for example, in cyclophanes, consists of two distinct physical mechanisms: 1) a decrease in activation strain, as well as 2) an enhanced TS interaction, as follows from our quantum chemical activation–strain analyses. These two mechanisms may contribute to different extents for clearly identifiable reasons. Thus, the Diels–Alder barrier of aromatic dienes reacting with acetylene, for example, decreases from 37 to 24 to 17 kcal mol$^{-1}$ along the series benzene, 5[paracyclophane], and 5[metacyclophane]. While the reduced barrier in both cyclophanes is induced by structural distortion of the aromatic core, the reduced barrier in the reaction of [5]paracyclophane mainly stems from a more stabilizing TS interaction with the dienophile, whereas the further reduced barrier for [5]metacyclophane is primarily caused by lowering of the activation strain due to a favorable predistortion (see Scheme 3).

The short five-membered bridge of [5]metacyclophane pulls the two meta carbon atoms of the aromatic core together, and this causes the bond-forming carbon atoms to point out of the aromatic plane and towards the dienophile. This predistorted aromatic core closely resembles the TS geometry and leads to a reduced activation strain. The bridge in [5]paracyclophane, on the other hand, pulls the two para carbon atoms towards each other, whereas the bond-forming carbon atoms are left unaffected and as such not favorably predistorted, which is associated with a significantly smaller reduction in activation strain. Instead, [5]paracyclophane reacts more rapidly compared to benzene, due to the more stabilizing orbital interactions that arise from a distortion-induced decrease of the H–L gap within the diene. The latter is chiefly the result of the out-of-plane bending of the aromatic core induced by the oligomethylene bridge, which has, among others, the effect of destabilizing the $\pi$-HOMO due to an increase in antibonding $\pi_{p} - \pi_{p}$ overlap. Similar to [5]paracyclophane, the H–L gap also decreases within [5]metacyclophane, but this decrease is offset by an increase in the H–L gap within acetylene leading to larger donor–acceptor orbital-energy gaps, and thus less stabilizing orbital interactions, compared to the reaction of [5]paracyclophane.

Interestingly, the distortion-driven mechanisms discussed above can now also be addressed individually through different means. A reduced activation strain can be directly leveraged by employing a meta-connected cyclophane bridge. On the other hand, stronger interaction, originating from a much smaller H–L gap in [5]paracyclophane, can also be induced...
through, for example, main-group heteroatom substitution in [5]metacyclophane. As a proof-of-concept, the dually activated (reduced activation strain plus stronger interaction) M@P, featuring C–P bond formation in a meta-bridged phosphazenene has an aromatic Diels–Alder barrier of only 2 kcal mol\(^{-1}\), which is almost 35 kcal mol\(^{-1}\) lower than that of benzene. In this way, we highlight the ability to tune aromatic Diels–Alder cycloadditions by means of multiple activation channels. We envisage that this might also be utilized for the activation of small molecules.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: activation strain model • arenes • cycloaddition • cyclophanes • density functional calculations

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