

# Stabilizing a different cyclooctatetraene stereoisomer

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An unconventional *cis-cis-cis-trans* or (Z,Z,Z,E) structure **B** of cyclooctatetraene (COT) is calculated to lie only 23 kcal/mol above the well-known tub-shaped (Z,Z,Z,Z) isomer **A**; one example of this type of structure is known. The barrier for **B** returning to **A** is small, 3 kcal/mol. However, by suitable choice of substituents, the (Z,Z,Z,E) isomer can be made to lie in energy below the tub-shaped structure. Steric, clamping, and electronic strategies are proposed for achieving this. In the steric strategy, the C<sub>8</sub>H<sub>4</sub>(CH<sub>3</sub>)<sub>2</sub>(C<sup>t</sup>Bu)<sub>3</sub>)<sub>2</sub> structure **B** is predicted to lie 21 kcal/mol below structure **A**, which is separated from form **B** only by a small barrier. A simple clamping strategy, effective for COT planarization, does not influence the A/B isomerization much. But, if the clamping group is aromatic (a fused benzene, pyrrole, thiophene, furan), the subtle interplay of potential aromaticity with clamping can be used to confer persistence if not stability on the (Z,Z,Z,E) isomer. An electronic strategy of a different kind, push-pull substitution on the COT ring, was not very effective in stabilizing the **B** form. However, it led us to vicinal amine-borane-substituted normal COTs that proved to be quite good at activating H<sub>2</sub> in a frustrated Lewis pair scenario.

cyclooctatetraene | steric effects | electronic effects | frustrated Lewis pair | molecular orbital theory

Cyclooctatetraene (COT) was first synthesized (1) in 1911. The molecule is most certainly not aromatic, in accord with Hückel's rule (2). It features four *cis*- or *Z* double bonds in a characteristic nonplanar *D*<sub>2d</sub> tub shape (3). From a combined femtosecond rotational coherence spectroscopy and theoretical study we have the molecule's precise gas-phase structure, with bond lengths *r*<sub>c</sub>(C–C) = 1.470, *r*<sub>c</sub>(C=C) = 1.337, and *r*<sub>c</sub>(C–H) = 1.079 Å (4). Potential ring inversion and bond-bond switching in COT have fascinated the organic community for decades (5–7). The planar *D*<sub>4h</sub> structure of COT is a transition state (TS) for the ring inversion (calculated barrier height of 10–14 kcal/mol) (8–12). The *D*<sub>8h</sub> bond-switching TS lies a few kilocalories per mole higher. The accepted automerization surface is summarized schematically in Fig. 1.

Motivated by the recent determination of the structures of some asymmetrically substituted COTs (13), we began a systematic study of COTs. Some peculiar geometries, far away from the tub shape, emerged; in time we identified them as *cis-cis-cis-trans* (Z,Z,Z,E) isomers of COT. Stabilizing these structures is the aim of this article.

(Z,Z,Z,E)-COT structures already appear in the theoretical and experimental literature. Conesa and Rzepa in 1998 predicted this isomer to lie 21–29 kcal/mol above the conventional all-*Z* structure, with a small barrier to return to all-*Z* COT (14). In their studies of Möbius aromaticity, Havenith et al. (15) optimized a C<sub>8</sub>H<sub>8</sub> (Z,Z,Z,E) structure, finding it again 21–29 kcal/mol above (Z,Z,Z,Z). And, in a comprehensive paper on the photochemistry and thermal rearrangements of COT, Garavelli et al. (16) found the (Z,Z,Z,E) isomer as a reaction intermediate, 24 to 25 kcal/mol above normal COT. The primary interest in their wide-ranging paper was in the photochemistry of C<sub>8</sub>H<sub>8</sub>.

Experimentally, a synthesis of a probable (Z,Z,Z,E) isomer was cautiously forwarded by White et al. (17). And, a dibenzannelated derivative has been synthesized by Carnes et al. (18), with its crystal structure determined. The (Z,Z,Z,E) isomer has also been mentioned in several papers (19, 20).

## (Z,Z,Z,E)-COT

**A Second COT Isomer.** As did the above-cited authors, we located the (Z,Z,Z,E) isomer of COT (**B**) as a local minimum on its potential energy surface. Throughout this paper, we use the ωB97X-D/cc-pVTZ (density functional theory method using the ωB97X-D functional with correlation-consistent polarized valence triple-zeta basis set) method of calculation (details are provided in *SI Appendix*) unless otherwise noted). The structure of **B** is shown in Fig. 2, along with the calculated equilibrium structure of the normal all-*Z* isomer (**A**). The geometry of **B** predicted by us does not differ markedly from those computed earlier (15, 16), and the energy, +23 kcal/mol relative to **A**, is also similar. The geometry also matches that of the dibenzannelated isomer whose structure is known (18).

The (Z,Z,Z,E) structure is strained. The large deviation from the optimal angle at an sp<sup>2</sup> carbon in **B** (C2–C1–C8 114°, C1–C8–C7 128°, and C8–C7–C6 139°) reflects the higher energy of **B** relative to **A**. If one looks at a side view, sighting along the E double-bond carbons (Fig. 2, *Bottom*), one sees clearly the effect of the eight-membered ring constraint: the C1–C2–C3–C4 dihedral angle is 130°. If one were to take a model E-1,2-dimethylethylene (E-2-butene), and distort it to this dihedral angle, the energetic cost would be 13 kcal/mol.

While there is definite bond alternation in **B**, the double and single bond lengths are somewhat more equalized than in **A**. And, six of the carbon atoms, in the Z,Z,Z part of **B**, are pretty much coplanar. **B** is clearly chiral.

We have not yet studied the remaining COT isomers, especially the fascinating (Z,E,Z,E) one (14, 16, 21). Our structure search in the Cambridge Structural Database (CSD) revealed a subunit in the structure of 9,9',10,10'-tetrahydrodianthracene that resembles the (Z,E,Z,E)-COT structure (22). The CSD also contains one fascinating molecule, a di-Fe(CO)<sub>3</sub> complex of COT that approximates this geometry (23), but the organometallic bonding naturally changes the bonding picture. We also have not yet studied the possible products of intramolecular rearrangement [which play such an interesting role in the chemistry of the (Z,Z,Z,Z) form (14, 16)] of the **B** isomer.

## Significance

Cyclooctatetraene (COT) is a poster child for nonaromatic molecules. An isomer of tub-shaped COT, with one of the ring double bonds changed from the usual *cis* form to a *trans* one, lies some 23 kcal/mol higher in energy. Devising a substitution strategy for turning the tables, making the *trans* isomer the stable point of the system, is the challenge. Simple bonding ideas, of the bulk of substituents, of clamping and turning aromaticity on and off, of pushing electrons in and out of the system, guide us in devising several realistic candidates. Along the way, a set of molecules that might easily split hydrogen reversibly emerges.

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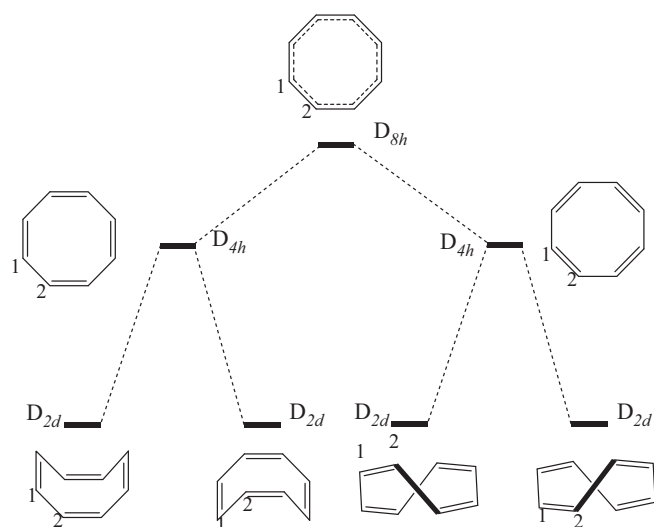


Fig. 1. Accepted mechanism for automerization of  $D_{2d}$  all-Z COT.

**The  $C_8H_8$  (Z,Z,Z,E) Structure Is Evanescent.** As shown in Fig. 2, the transition state for **B** going to **A** lies only 3 kcal/mol above structure **B**. This result was qualitatively confirmed with three other density functionals, and was also obtained in earlier studies (14, 16). There would barely be a chance for low-temperature matrix isolation of the (Z,Z,Z,E) isomer. The situation is changed for the dibenzan-related compound (18); while it is thermodynamically unstable, it is reasonably persistent, sufficiently so to allow a crystal structure determination.

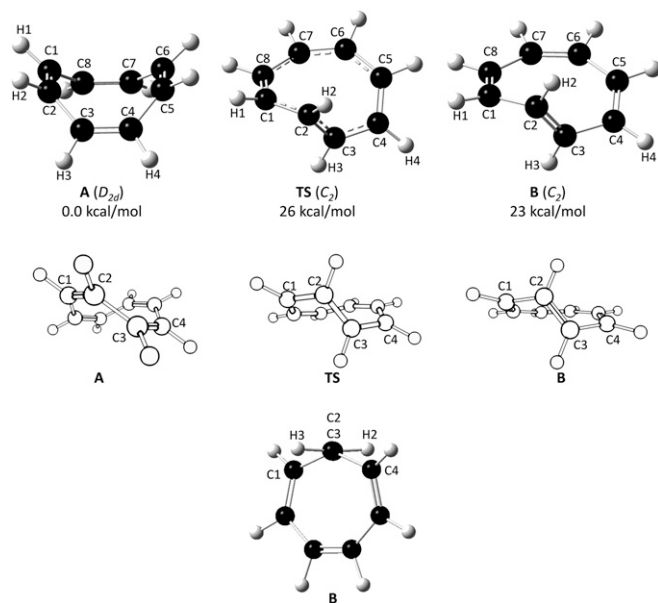


Fig. 2. Isomerization of the unsubstituted COT structure **A** to **B** through transition state **TS**, in three views: at an angle at the top, in a side view in the middle, and sighting along C2–C3 at the bottom. The calculated bond distances that follow are in angstroms, dihedral angles in degrees: **A**: C1–C2: 1.33; C2–C3: 1.47; C3–C4: 1.33; C4–C5: 1.47; C5–C6: 1.33; C6–C7: 1.47; C7–C8: 1.33; C8–C1: 1.47; H1–C1–C2–H2: 0°; H2–C2–C3–H3: 46°. **TS**: C1–C2: 1.40; C2–C3: 1.39; C3–C4: 1.40; C4–C5: 1.38; C5–C6: 1.43; C6–C7: 1.39; C7–C8: 1.43; C8–C1: 1.38; H1–C1–C2–H2: 43°; H2–C2–C3–H3: 141°. **B**: C1–C2: 1.45; C2–C3: 1.34; C3–C4: 1.45; C4–C5: 1.34; C5–C6: 1.47; C6–C7: 1.36; C7–C8: 1.47; C8–C1: 1.34; H1–C1–C2–H2: 77°; H2–C2–C3–H3: 174°.

Table 1. Relative energies (kilocalories per mole) of structures **A** (the Z,Z,Z,Z COT), **B** (Z,Z,Z,E COT), and the TS between these, for the parent and substituted COT molecules;  $R^1$  is the substituent on C1,  $R^2$  on C2,  $R^3$  on C3, and  $R^4$  on C4

Molecules	$R^1$	$R^2$	$R^3$	$R^4$	<b>A</b>	<b>B</b>	<b>TS</b>
1	H	H	H	H	0	23	26
2	CH <sub>3</sub>	CH <sub>3</sub>	H	H	0	18	23
3	<sup>t</sup> Bu	H	H	<sup>t</sup> Bu	0	17	24
4	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	0	12	20
5	<sup>t</sup> Bu	CH <sub>3</sub>	CH <sub>3</sub>	<sup>t</sup> Bu	0	3	14
6	C( <sup>t</sup> Bu) <sub>3</sub>	H	H	C( <sup>t</sup> Bu) <sub>3</sub>	0	1	4
7	Si(Si(CH <sub>3</sub> ) <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	Si(Si(CH <sub>3</sub> ) <sub>3</sub> ) <sub>3</sub>	0	–2	10
8	C(Si(CH <sub>3</sub> ) <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	C(Si(CH <sub>3</sub> ) <sub>3</sub> ) <sub>3</sub>	0	–12	7
9	Si( <sup>t</sup> Bu) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	Si( <sup>t</sup> Bu) <sub>3</sub>	0	–17	2
10	C( <sup>t</sup> Bu) <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	C( <sup>t</sup> Bu) <sub>3</sub>	0	–21	4

The reference energy in each case is that of the **A** form.

**The Transformation (Z,Z,Z,E) ↔ (Z,Z,Z,Z) also Interchanges Single and Double Bonds.** As Fig. 2 (Middle) shows clearly, the single bond C2–C3 (1.47 Å) in **A** changes into a *trans* (E) double bond (1.34 Å) in **B**. The other three single bonds in **A** change into *cis* (Z) double bonds in **B**. The four *cis* double bonds in **A** become single bonds in **B** in the process of isomerization. If the resulting molecule would be the same as the original one, this would be called an automerization. A facile sequence of (Z,Z,Z,Z) → (Z,Z,Z,E) → (Z,Z,Z,Z) transformations, as interesting as it is, would return an all-Z COT to itself, not shifting the double bonds, nor would it invert the ring.

#### Can One Make the (Z,Z,Z,E) Isomer the Stable Form of a Substituted COT?

**The Steric Strategy.** The dihedral angle H2–C2–C3–H3 changes from 46° in **A** to 174° in **B**, and the dihedral angle H1–C1–C2–H2 rotates from 0° in **A** to 77° in **B**. These features, as well as examination of models, point to a reduced steric interaction between substituents at positions H1, H2, H3, and H4 in **B**, and suggest a steric strategy for stabilizing the (Z,Z,Z,E) isomer. What is needed are sterically demanding substituents at these positions.

Table 1 shows a series of **B** structures with computed energies in the range –21 to +23 kcal/mol relative to **A**. We used our standard ωB97X-D/cc-pVTZ method for the smaller molecules (the first five rows), and ωB97X-D/6–31G\* (see *SI Appendix* for methodology) for the others. The results were checked with

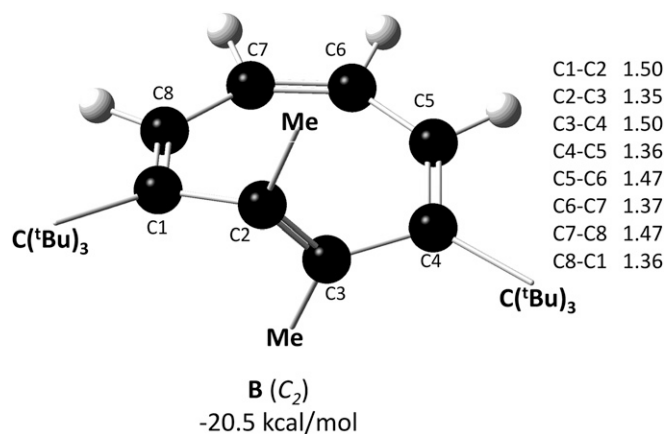


Fig. 3. Most favorable structure of type **B** (Z,Z,Z,E isomer of COT), **B10**, among the sterically hindered substituted molecules considered. This structure is predicted to lie 21 kcal/mol below the conventional (Z,Z,Z,Z) tub-shaped structure of COT. The bond lengths are given in angstroms.

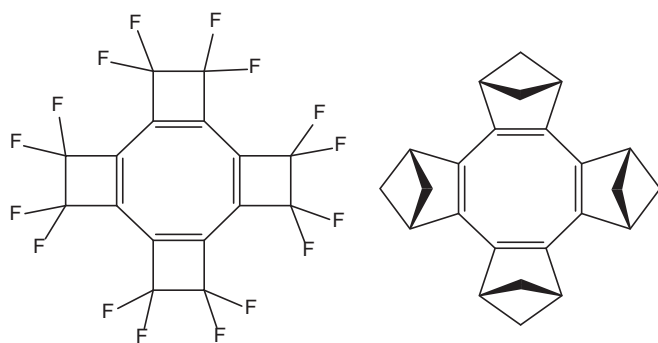


Fig. 4. Some known COTs planarized by a clamping strategy.

several methods; the absence of multireference character was confirmed with some diagnostics (*SI Appendix*).

Table 1 confirms the validity of the strategy. Methyl groups at positions 1 and 2, or at positions 1, 2, 3, and 4 reduce the preference for **A** (entries 2 and 4); *t*-butyl groups at positions 1 and 4 (entries 3 and 5) reduce it further. The still larger substituents (entries 7–10) turn the conformational preference around—the (*Z,Z,Z,E*) isomer, **B**, is energetically favored for these. The calculated activation energies for transformations from the higher energy isomer (**A** → **B** or **B** → **A**) are low, never exceeding 11 kcal/mol.

Fig. 3 shows the ring geometry of our “best” result, molecule **10** in Table 1. For this molecule, not only will the (*Z,Z,Z,E*) isomer **B10** be lower in energy, but, given the small theoretical activation energy for isomerization, the “normal” (*Z,Z,Z,Z*) structure **A10** should not persist at ambient conditions.

**Clamping and Aromaticity.** For normal (*Z,Z,Z,Z*) COT, strategies for planarization and enhancing bond shifts have a venerable history. Important in this story is a theoretical design paper by Baldrige and Siegel (24), the independent synthesis of some planar COTs (25, 26), shown in Fig. 4, some others in which the aromaticity of fused rings is balanced with steric and electronic

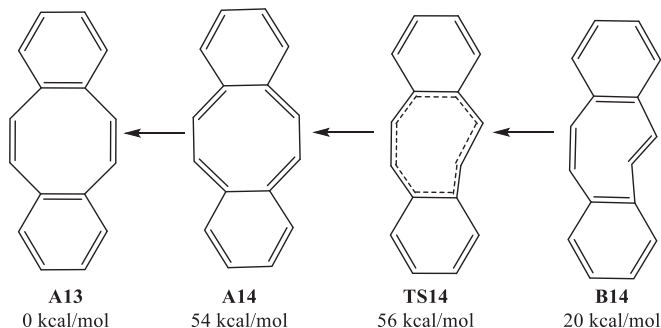
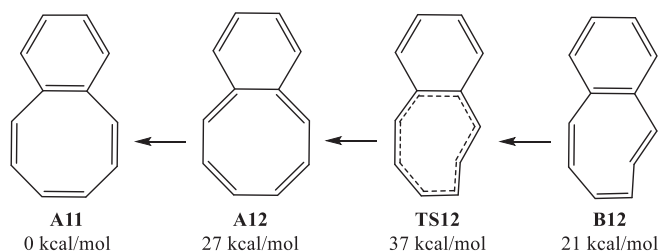


Fig. 5. COT molecules with one and two benzene clamping rings; the energies are relative to **A11** and **A13**, respectively.

constraints (27), and related theoretical work (28–30). There are a number of other planarized COTs, not mentioned here.

We tried to implement a simple clamping strategy to stabilize **B** isomers, by examining the effect of four- and five-membered exocyclic saturated rings, similar to those shown in Fig. 4. The idea is to fuse small exocyclic rings to the single bonds in **A**, for instance, at the C2–C3 or C6–C7 positions. Considering the noncoplanarity of the attachment bonds at these positions, it is hoped that the strain introduced by small exocyclic rings would destabilize **A**. The single bonds in **A** turn into double bonds in **B**; small rings fused to double bonds are expected to engender less strain, thus stabilizing **B**. These attempts were not particularly successful; details are provided in *SI Appendix*.

We decided to raise the stakes for departure from planarity, by making the exocyclic ring aromatic, as in benzene, pyrrole, furan, or thiophene. We discuss in the text benzene- and pyrrole-fused COT; calculations on furan- and thiophene-fused COT are given in *SI Appendix*.

Single benzannulation of normal COT leads to the isomer **A11** and **A12** (Fig. 5), the former, which retains aromaticity in its benzene ring, naturally at lower energy. Among a number of isomers, the lowest-energy benzannulated (*Z,Z,Z,E*) isomer is **B12**. A pathway for the **B12** to **A11** isomerization, passing through **A12** (and involving two bond-shift steps), encounters an activation barrier of at least 16 kcal/mol. Another potential path—single step, direct rotation around the E double bond—is not that simple to model, but we think it will encounter a higher activation energy.

With two nonadjacent benzene rings, the system synthesized by the Nuckolls and Steigerwald group, the most stable isomers are **A13** and **B14** (Fig. 5). The adjacent benzene isomers, as well as nonaromatic variants, are described in *SI Appendix*. The energy difference between **B14** and **A13** is roughly that calculated earlier (18). The possible mechanisms of conversion of **B14** to the more stable **A13** parallel those mentioned in the monobenzo case. But, now the potential intermediate **A14** is at much higher energy, as two aromatic rings are lost in it. This would provide **B14** (the molecule synthesized) with greater kinetic stability than **B12**.

The pyrrole story has similar features, with a complex interplay of clamping, aromaticity, and a variety of pathways for transformation. Fig. 6 shows the most stable (*Z,Z,Z,Z*) and (*Z,Z,Z,E*) isomers for two potential placements of the NH group [analogous to the fascinating benzopyrrole and isobenzopyrrole story (31–33)]. Looking only at the most stable isomers in each series, we find that the (*Z,Z,Z,Z*) isomers are again around 20 kcal/mol lower in energy. Considerations in *SI Appendix* point to greater kinetic persistence for a hypothetical **B18** compared with **B16**.

To summarize, using aromaticity and clamping one does not enhance the stability of the (*Z,Z,Z,E*) isomers. But, the strategy gains kinetic persistence for these metastable species.

**An Electronic Strategy.** There is a long history of reducing the strength of the  $\pi$ -component of double bonds by a substitution pattern such as DDC=CAA, where D is a  $\pi$ -donor ( $\text{NH}_2$ , OH, halogen), and A a  $\pi$ -acceptor (CN, COH,  $\text{BH}_2$ ,  $\text{CF}_3$ ). The donor and acceptor substituents stabilize respective partial positive and negative

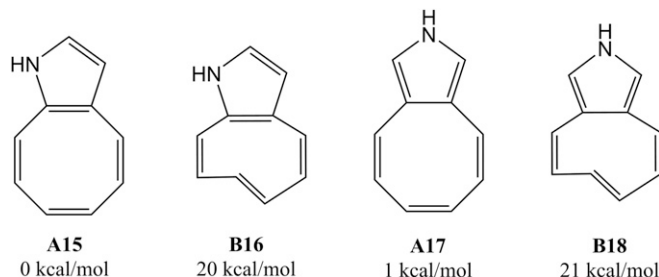


Fig. 6. COT molecules with a pyrrole clamping ring. The energies are relative to **A15**.

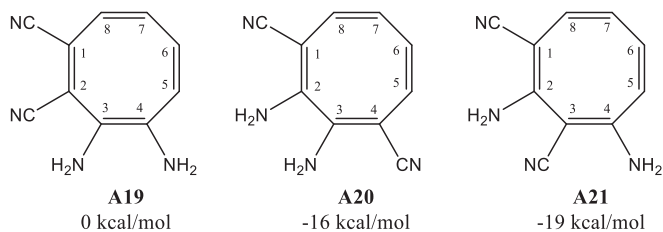


Fig. 7. Structures of **A19**, **A20**, and **A21**. The energies are relative to **A19**.

ion character on the carbons they bond to, and thereby entail a zwitterionic contribution at the expense of the covalent  $\pi$ -bond (34–37). The argument given is basically a valence bond theory one; a molecular orbital explanation of the effect of these “push–pull” systems may also be provided. Note that while the substituted ethylene  $\pi$ -bond strength is reduced, the ethylene is overall stabilized by such a pattern of substitution, by interactions of the donor and acceptor orbitals with ethylene  $\pi$  and  $\pi^*$ . We thought we might make use of this strategy to induce an **A**-to-**B** transformation.

We first studied the influence of the push–pull effect on the stability of COT, using  $-\text{CN}$  as a  $\pi$ -acceptor, and  $-\text{NH}_2$  as a  $\pi$ -donor. As shown in Fig. 7, **A20** and **A21** are substantially stabilized if the push–pull pattern is adopted.

But, what is the effect of the push–pull substitution on the relative **A** and **B** stability and interconversion? Fig. 8 shows that the isomerization of **A19** to **B19** (one could think of this as push–push + pull–pull  $\rightarrow$   $2 \times$  push–pull; in **B**, one push–pull is through a *trans* double bond and the other through three conjugated double bonds) was predicted to be endothermic by only 4 kcal/mol. The energy barrier (**TS19**) is 10 kcal/mol. The (*Z,Z,Z,E*) structures for **B20** and **B21** were not found to be local minima; they collapsed back to their respective **A** isomers. This is understandable for **B20**, which would have two donor substituents on the *E* double bond. But, we do not yet understand why **B21** is destabilized.

The additional molecules reported in Table 2 support application of this electronic strategy (the numbering refers to the common structure shown in Fig. 3). Compared with  $-\text{CN}$  and  $-\text{NO}_2$ , the  $-\text{BH}_2$  group may be the stronger  $\pi$ -acceptor, with the lower energy of the (*Z,Z,Z,E*) isomer **22–24**. The stronger  $\pi$ -donor  $\text{N}(\text{CH}_3)_2$  in **25**, or the stronger  $\pi$ -acceptor  $\text{B}(\text{CF}_3)_2$  in **26**, enhances the push–pull effect to favor the (*Z,Z,Z,E*) isomer. Overall the push–pull strategy helps to stabilize the **B** form. But, in the end it proves difficult with this approach to turn the conformational preference around, to favor the (*Z,Z,Z,E*) isomer.

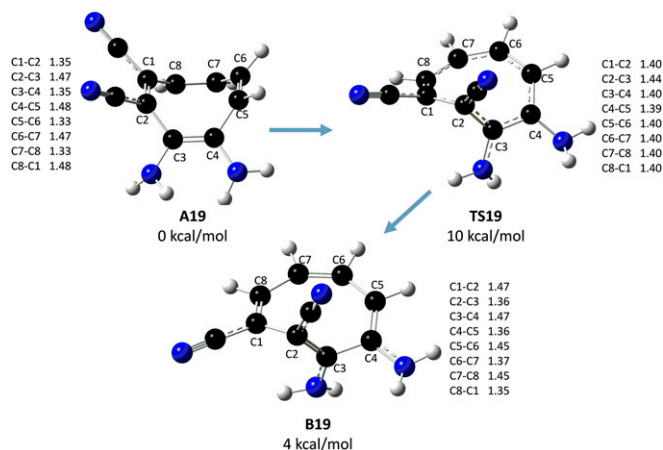


Fig. 8. Structures of **A19**, **TS19**, and **B19** with  $-\text{CN}$  and  $-\text{NH}_2$  groups. The lengths are in angstroms.

Table 2. Relative energies (in kilocalories per mole; calculated with the  $\omega$ B97X-D/cc-pVTZ method) of structures **A**, **B**, and **TS** for COT molecules with donor and acceptor substituents

Molecules	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	<b>A</b>	<b>B</b>	<b>TS</b>
<b>22</b>	H	CN	NH <sub>2</sub>	H	0	14	15
<b>23</b>	H	NO <sub>2</sub>	NH <sub>2</sub>	H	0	11	14
<b>24</b>	H	BH <sub>2</sub>	NH <sub>2</sub>	H	0	9	10
<b>25</b>	H	BH <sub>2</sub>	N(CH <sub>3</sub> ) <sub>2</sub>	H	0	6	7
<b>26</b>	H	B(CF <sub>3</sub> ) <sub>2</sub>	NH <sub>2</sub>	H	0	3	4

### Sideways Step to Frustrated Lewis Pairs

For some of the molecules we studied (**A22**, **A23**, and **A24** in Table 2), we found that their geometry optimization, starting with slightly different initial geometries, led to structures quite different from those we have studied so far. A full B–N bond was formed, as shown in **C22**, **C23**, and **C24** in Fig. 9. Once observed (theoretically), with awareness of the chemistry of aminoboranes ( $\text{H}_3\text{NBH}_3$ ) and related compounds, this made sense.

The isomerizations from **A24**, **25**, **26** to **C24**, **25**, **26** are all calculated to be facile, with activation energies of 5, 3, and 1 kcal/mol, respectively. This implies an interestingly fast equilibrium for **A24/C24**, and facile rearrangement to the four-membered-ring form for **A25** and **A26**.

The full B–N bond formation reminded us of the remarkable story of frustrated Lewis pairs (FLPs), pioneered by Stephan (38). The most interesting thing about these molecules is that they are reactive, activating  $\text{H}_2$  and other bonds heterolytically. Linked amine–borane units have so far been relatively rare in FLP chemistry, but they are known (39–42). We were thus encouraged to study the interaction of our substituted COTs with  $\text{H}_2$ .

There have been many calculations on FLPs and the mode of their reaction with  $\text{H}_2$  (43–46). For instance, Zeonjuk et al. (47) investigated six combinations of Lewis acids (boranes) and Lewis bases (phosphines) that showed different reactivity in  $\text{H}_2$  activation. One of them,  $\text{tBu}_3\text{P}$  plus  $\text{B}(p\text{-C}_6\text{F}_4\text{H})_3$ , could catalyze reversible hydrogen activation, with a Gibbs energy barrier of 22.6 kcal/mol in solvent, and an exothermicity of 0.3 kcal/mol. In the context of B,*N*-based FLPs, Yepes et al. (48) studied the hydrogen activation by the geminal aminoborane-based frustrated Lewis pairs ( $\text{R}_2\text{N}-\text{CH}_2-\text{BR}'_2$ ). The reaction proceeds via a direct  $\text{H}_2$  splitting between B and N atoms, without prior  $\text{H}_2$  coordination. The activation barrier of the reaction depends strongly on the nature of the substituents on the acid or the base centers of the FLPs.

We studied the reactions of  $\text{H}_2$  with several lightly substituted (*Z,Z,Z,Z*) COT molecules, with  $\text{BR}_2$  and  $\text{NR}_2$  at the C2 and C3 positions. The COT skeleton provides the possibility to introduce R<sup>1</sup> and R<sup>4</sup> substituents as well, so that one can stabilize the generated cation–anion pair ( $-\text{NH}_3^+$  and  $-\text{BH}_3^-$ ) to facilitate the reaction.

Fig. 10 shows the calculated reaction path. **A24**, the molecule with one  $\text{BH}_2$  and one  $\text{NH}_2$  group, originally has these groups conjugated (coplanar) with their respective double bonds. Please

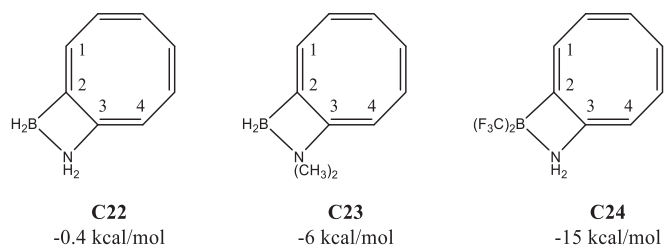


Fig. 9. Structures of **C24**, **C25**, and **C26**. The energies are relative to the structures labeled **A** in Table 2.

recall that the ring-closed form is 0.4 kcal/mol lower in energy, with a small activation energy to reaching it. The reaction begins with a H<sub>2</sub> coordinating mainly to the BH<sub>2</sub> substituent. However, the hydrogen molecule does not coordinate to the borane center in the absence of the -NH<sub>2</sub> group (i.e., R<sup>2</sup> = BH<sub>2</sub>, R<sup>3</sup> = H). Thus, even though intermediate **A24**•H<sub>2</sub> looks to be boron-coordinated, the adjacent NH<sub>2</sub> group is essential. The coordinated hydrogen molecule is slightly stretched, to 0.79 Å. From there the reaction proceeds through **TS24** (the H-H bond is stretched to 0.99 Å), only 7 kcal/mole higher at +21 kcal/mol, then on to product **A24**•H<sup>+</sup>H<sup>-</sup>. The product is quite unstable; both its stability and the energy of the TS can be tuned by substituents at C1 and C4 (*SI Appendix*).

Following the suggestion of H.R., we calculated dipole moments of molecule **A** and **B** 22–26. The dipole moments are substantial (1.7–4.9 D for the **A** series, 2–4 D larger for the **B** series). The effect of solvent on the reaction of **A22** and **A25** was then studied with an effective medium method for polar and nonpolar solvent. The results are shown in *SI Appendix*; ΔE and ΔG are reduced by 2–4 kcal/mol relative to the gas phase, but our conclusions remain qualitatively unchanged.

Playing with rigidity and clamping, we next tried some molecules in which the amine is replaced by a pyridine, and (separately or simultaneously) the borane made part of a five-membered ring. The molecules are **A27**, **A28**, and **A29**, and the theoretical energy profiles for these are shown in Fig. 11. The effect of solvent is analyzed in *SI Appendix*. As one might expect, the more polar the solvent, the more is the zwitterionic product stabilized. Note that the double clamping prevents the formation of the four-membered ring, so that **28** and **29** remain in the **A** form.

For **A28** and **A29** (a fluorinated derivative), the products of hydrogen activation are stabilized (relative to the cases studied above) and the activation energies are also relatively low. These model molecules constitute potential reversible hydrogen storage systems.

## Conclusion

The (Z,Z,Z,E) isomer of cyclooctatetraene, **B**, is calculated (by us and others) as 23 kcal/mol above the normal tub-shaped (Z,Z,Z,Z) isomer **A**, which has been with us for just over a century. **B** has tiny activation energy for transformation to **A**. To tinker with these energetics is a challenge to theory.

The first approach to stabilizing the mono-E isomer is a simple steric one. It is derived from observing that the isomerization is

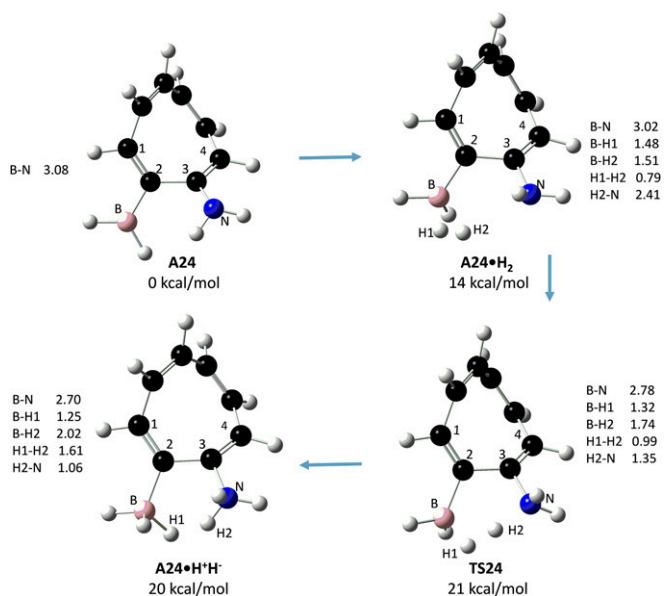


Fig. 10. Structures of **A24**, **A24**•H<sub>2</sub>, **TS24**, and **A24**•H<sup>+</sup>H<sup>-</sup>. The energies are relative to **A24**. The lengths are in angstroms.

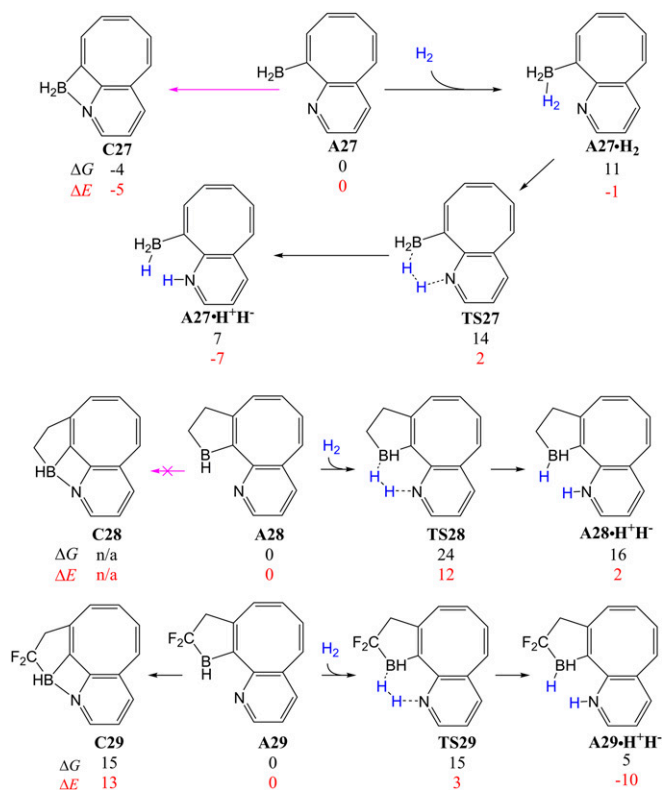


Fig. 11. Hydrogen activation profiles in N- and B-substituted COTs. The energies are relative to **A** (n/a denotes not available) in kilocalories per mole.

also a bond-shift process, single bonds converted into double bonds and vice versa, and that some dihedral angles (and with them steric encumbrance of substituents) change drastically. Bulky substituents at carbons that are involved in such drastic dihedral angle change, for instance, carbons 2 and 3, flanking the single bond of **A** that will become the E double bond in **B**, create a preference for **B**.

A clamping strategy, effective for planarizing COT, does not get us as far as the relative stabilization of **B**. However, if the clamping ring is potentially an aromatic one, as in the case of benzene, pyrrole, furan, and thiophene, the (Z,Z,Z,E) isomer gains in kinetic persistence if not thermodynamic stability.

Next we tried push-pull substitution of the COT ring with π-donors or -acceptors. This could bring the energy of the **B** form down (for instance with -CN at positions 1,2, and -NH<sub>2</sub> at 3,4), but we could not make the equilibrium shift predominantly toward **B**.

The electronic strategy, substitution by donors and acceptors, did show a reaction channel, the formation of a direct bond (BN in the case of amino and borane) between the substituents. This led us to connect the compounds in question to the burgeoning field of frustrated Lewis pairs and their heterolytic cleavage of molecular hydrogen. With no relation to the A-B isomerization, yet importantly connected to the stereochemical constraints operative in the COT skeleton, we found an ideal path for potentially reversible H<sub>2</sub> activation in some amino- and borane-substituted COTs.

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- Willstätter P, Waser E (1911) Über cyclo-octatetraen. *Chem Ber* 44:3423–3445.
- Wu JIC, Schleyer Pv R (2013) Hyperconjugation in hydrocarbons: Not just a “mild sort of conjugation.” *Pure Appl Chem* 85:1365–3075.
- Kaufman HS, Fankuchen I, Mark H (1948) Structure of cyclo-octatetraene. *Nature* 161: 165–165.
- Kummlı DS, Lobsiger S, Frey HM, Leutwyler S, Stanton JF (2008) Accurate determination of the structure of cyclooctatetraene by femtosecond rotational coherence spectroscopy and ab initio calculations. *J Phys Chem A* 112:9134–9143.
- Hopf H (2000) *Classics in Hydrocarbon Chemistry* (Wiley, Weinheim, Germany), pp 209–218.
- Minkin VI, Glukhovtsev MN, Simkin BYa (1994) *Aromaticity and Antiaromaticity* (Wiley, New York), pp 165–171.
- Williams RV (2009) *Strained Hydrocarbons: Beyond the van't Hoff and Le Bel Hypothesis*, ed Dodziuk H (Wiley, Weinheim, Germany), pp 403–411.
- Wenthold PG, Hrovat DA, Borden WT, Lineberger WC (1996) Transition-state spectroscopy of cyclooctatetraene. *Science* 272:1456–1459.
- Schild A, Paulus B (2013) Multireference calculations for ring inversion and double bond shifting in cyclooctatetraene. *J Comput Chem* 34:1393–1397.
- Hrovat DA, Borden WT (1992) CAS/SCF calculations find that a  $D_{8h}$  geometry is the transition state for double bond shifting in cyclooctatetraene. *J Am Chem Soc* 114: 5879–5881.
- Stevenson CD, Brown EC, Hrovat DA, Borden WT (1998) Isotope effects on the ring inversion of cyclooctatetraene. *J Am Chem Soc* 120:8864–8867.
- Andrés JL, Castaño O, Morreale A, Palmeiro R, Gomperts R (1998) Potential energy surface of cyclooctatetraene. *J Chem Phys* 108:203–207.
- Blouin S, Gandon V, Blond G, Suffert J (2016) Synthesis of cyclooctatetraenes through a palladium-catalyzed cascade reaction. *Angew Chem Int Ed Engl* 55:7208–7211.
- Conesa C, Rzepa HS (1998) PM3 and ab initio studies of the  $C_8H_8$  potential energy surface. Thermal isomerism of syn- and anti-tricyclo[4.2.0.0.2,5]octa-3,7-dienes. *J Chem Soc, Perkin Trans 2* 1998:857–862.
- Havenith RWA, van Lenthe JH, Jenneskens LW (2001) Möbius aromaticity in small [n] trans-annulenes? *Int J Quantum Chem* 85:52–60.
- Garavelli M, et al. (2002) Cyclooctatetraene computational photo- and thermal chemistry: A reactivity model for conjugated hydrocarbons. *J Am Chem Soc* 124: 13770–13789.
- White EH, Friend EW, Stern RL, Maskill H (1969) A probable trans-cyclooctatetraene. *J Am Chem Soc* 91:523–525.
- Carnes M, Buccella D, Decatur J, Steigerwald ML, Nuckolls C (2008) Helical (5Z, 11E)-dibenzo[a,e]cyclooctatetraene: A spring-loaded monomer. *Angew Chem Int Ed Engl* 47:2982–2985.
- Zimmerman HE, Iwamura H (1970) Thermal and photochemical interconversions of cyclooctatetraenes and semibullvalenes. Exploratory organic photochemistry. LII. *J Am Chem Soc* 92:2015–2022.
- Takayama J, Sugihara Y, Ishii A, Nakayama J (2003) Preparation of 1,4,5,8-tetra-tert-butyl-1,3,5,7-cyclooctatetraene by twofold  $SO_2$  extrusion. *Tetrahedron Lett* 44: 7893–7896.
- Dewar MJS, Merz KM (1985) Does chair cyclo-octatetraene exist? *J Chem Soc Chem Commun* 1985:343–344.
- Vivattene RL, Greene FD, Cheung LD, Majeste R, Trefonas LM (1974) 9,9',10,10'-Tetradehydrodianthracene. Formation, protection, and regeneration of a strained double bond. *J Am Chem Soc* 96:4342–4343.
- Dickens B, Lipscomb WN (1962) Molecular and valence structures of complexes of cyclo-octatetraene with iron tricarbonyl. *J Chem Phys* 37:2084–2093.
- Baldrige KK, Siegel JS (2001) Quantum mechanical designs toward planar delocalized cyclooctatetraene: A new target for synthesis. *J Am Chem Soc* 123:1755–1759.
- Einstein FW, Willis AC, Cullen WR, Soulen RL (1981) Perfluorotetracyclobutacyclooctatetraene; a planar eight-membered ring system; X-ray crystal structure. *J Chem Soc Chem Commun* 526–528.
- Matsuura A, Komatsu K (2001) Efficient synthesis of benzene and planar cyclooctatetraene fully annelated with bicyclo[2.1.1]hex-2-ene. *J Am Chem Soc* 123: 1768–1769.
- Hensel T, et al. (2013) Diazadioxo[8]circulenes: Planar antiaromatic cyclooctatetraenes. *Chemistry* 19:17097–17102.
- Fowler PW, Havenith RW, Jenneskens LW, Soncini A, Steiner E (2002) Paratropic delocalized ring currents in flattened cyclooctatetraene systems with bond alternation. *Angew Chem Int Ed Engl* 41:1558–1560.
- Nishinaga T, Ohmae T, Iyoda M (2010) Recent studies on the aromaticity and antiaromaticity of planar cyclooctatetraene. *Symmetry (Basel)* 2:76–97.
- Krygowski TM, Pindelska E, Cyranski MK, Häfeliinger G (2002) Planarization of 1,3,5,7-cyclooctatetraene as a result of a partial rehybridization at carbon atoms: An MP2/6-31G\* and B3LYP/6-311G\*\* study. *Chem Phys Lett* 359:158–162.
- Dewar MJS, Harget AJ, Trinjstić N, Worley SD (1970) Ground states of conjugated molecules. *Tetrahedron* 26:4505–4516.
- Jursic B (1996) The estimation of the aromaticity of five-membered and benzo-fused five-membered rings by the hybrid DFT computed magnetic properties. *J Heterocycl Chem* 33:1079–1081.
- Martínez A, Vázquez M-V, Carreón-Macedo JL, Sansores LE, Salcedo R (2003) Benzene fused five-membered heterocycles. A theoretical approach. *Tetrahedron* 59: 6415–6422.
- Raczyńska ED, Gal JF, Maria PC (2016) Enhanced basicity of push-pull nitrogen bases in the gas phase. *Chem Rev* 116:13454–13511.
- Varanasi PR, Jen AKY, Chandrasekhar J, Namboothiri INN, Rathna A (1996) The important role of heteroaromatics in the design of efficient second-order nonlinear optical molecules: Theoretical investigation on push-pull heteroaromatic stilbenes. *J Am Chem Soc* 118:12443–12448.
- Breslow R, Kivelevich D, Mitchell MJ, Fabian W, Wendel K (1965) Approaches to “push-pull” stabilized cyclobutadienes. *J Am Chem Soc* 87:5132–5139.
- Sandstrom J, Sjostrand U, Wennerbeck I (1977) Demonstration of fourfold rotational barriers in push-pull ethylenes. *J Am Chem Soc* 99:4526–4527.
- Stephan DW, Erker G (2010) Frustrated Lewis pairs: Metal-free hydrogen activation and more. *Angew Chem Int Ed Engl* 49:46–76.
- Sumerin V, et al. (2008) Molecular tweezers for hydrogen: Synthesis, characterization, and reactivity. *J Am Chem Soc* 130:14117–14119.
- Sumerin V, et al. (2008) Facile heterolytic  $H_2$  activation by amines and  $B(C_6F_5)_3$ . *Angew Chem Int Ed Engl* 47:6001–6003.
- Mo Z, Rit A, Campos J, Kolychev EL, Aldridge S (2016) Catalytic B-N dehydrogenation using frustrated Lewis pairs: Evidence for a chain-growth coupling mechanism. *J Am Chem Soc* 138:3306–3309.
- Appelt C, Slootweg JC, Lammertsma K, Uhl W (2013) Reaction of a P/Al-based frustrated Lewis pair with ammonia, borane, and amine-boranes: Adduct formation and catalytic dehydrogenation. *Angew Chem Int Ed Engl* 52:4256–4259.
- Rokob TA, Hamza A, Stirling A, Soós T, Pápai I (2008) Turning frustration into bond activation: A theoretical mechanistic study on heterolytic hydrogen splitting by frustrated Lewis pairs. *Angew Chem Int Ed Engl* 47:2435–2438.
- Rokob TA, Hamza A, Stirling A, Pápai I (2009) On the mechanism of  $B(C_6F_5)_3$ -catalyzed direct hydrogenation of imines: Inherent and thermally induced frustration. *J Am Chem Soc* 131:2029–2036.
- Sumerin V, et al. (2009) Experimental and theoretical treatment of hydrogen splitting and storage in boron-nitrogen systems. *J Org Chem* 69:2654–2660.
- Wang K, Tang K, Zhang J-G (2016) A theoretical investigation of the frustrated Lewis pairs of C/P and B/N in the metal-free hydrogen-storage compounds. *Int J Hydrogen Energy* 41:18963–18970.
- Zeonjuk LL, et al. (2013) On the mechanism of hydrogen activation by frustrated Lewis pairs. *Chemistry* 19:17413–17424.
- Yepes D, Jaque P, Fernández I (2016) Deeper insight into the factors controlling  $H_2$  activation by geminal aminoborane-based frustrated Lewis pairs. *Chemistry* 22: 18801–18809.