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\textsubscript{6}H\textsubscript{4}(CH\textsubscript{3})(C\textsubscript{2}H\textsubscript{5})\textsubscript{3} structure B is predicted to lie 21 kcal/mol below structure A, which is separated from B form 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 steric effects 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 dibenzanellated isomer whose structure is known (18).

The (Z,Z,Z,E) structure is strained. The large deviation from the optimal angle at an sp\textsuperscript{2} carbon in B (C–C–C 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-tetrahydrodianthrancene that resembles the (Z,E,Z,E)-COT structure (22). The CSD also contains one fascinating molecule, a di-Fe(CO)\textsubscript{3} 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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The \( C_6H_8 \) (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 dibenzannellated compound (18); while it is thermodynamically unstable, it is reasonably persistent, sufficiently so to allow a crystal structure determination.

The transformation \( (Z,Z,Z,E) \rightarrow (Z,Z,Z,Z) \) 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 \( (Z,Z,Z,Z) \rightarrow (Z,Z,Z,E) \rightarrow (Z,Z,Z,Z) \) 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. 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

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<th>( R^3 )</th>
<th>( R^4 )</th>
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<th>B</th>
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The reference energy in each case is that of the A form.

The Transformation \( (Z,Z,Z,E) \rightarrow (Z,Z,Z,Z) \) 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 \( \omega B97X-D/cc-pVTZ \) method for the smaller molecules (the first five rows), and \( \omega B97X-D/6-31G^* \) (see SI Appendix for methodology) for the others. The results were checked with...
COT molecules with one and two benzene clamping rings; the en-
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| A13
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| A
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Several known COTs planarized by a clamping strategy. Compared with A13 and A10 B16 B12 B should not persist at ambient conditions. Is energetically favored for or and to the more in Table 1. For this molecule, not only will the (Z,Z,Z,E) isomer, B, be at much higher energy, as A12 t is roughly that calculated earlier –– to (and π point to greater A11 (Z,Z,Z,Z) (Fig. 5). The adjacent benzene isomers, as well as (entries 2 and 4); 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 Baldridge 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 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 benzannelation 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 benzannelated (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 in this 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.

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

Fig. 6. COT molecules with a pyrrole clamping ring. The energies are relative to A15.
ion character on the carbons they bond to, and thereby entail a zwitterionic contribution at the expense of the covalent π-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 π-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 π and π*.

We first studied the influence of the push–pull effect on the stability of COT, using -CN as a π-acceptor, and -NH₂ as a π-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 → 2 × 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 -CN and -NO₂, the -BH₂ group may be the stronger π-acceptor, with the lower energy of the (Z,Z,Z,E) isomer 22–24. The stronger π-donor N(CH₃)₂ in 25, or the stronger π-acceptor B(CF₃)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.

### Table 2. Relative energies (in kilocalories per mole; calculated with the oB97X-D/cc-pVTZ method) of structures A, B, and TS for COT molecules with donor and acceptor substituents

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### 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 (H₂NBH₃) 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 3, 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 H₂ 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 H₂.

There have been many calculations on FLPs and the mode of their reaction with H₂ (43–46). For instance, Zeonjuk et al. (47) investigated six combinations of Lewis acids (boranes) and Lewis bases (phosphines) that showed different reactivity in H₂ activation. One of them, Bu₃P plus B(p-C₆H₄H₃), could catalyze reversible hydrogen activation, with a Gibbs energy barrier of 22.6 kcal/mol in solvent, and an exothermicity of 0.5 kcal/mol. In the context of B₃N-based FLPs, Yepes et al. (48) studied the hydrogen activation by the geminal aminoborane-based frustrated Lewis pairs (R₃N–CH₂–BR₃). The reaction proceeds via a direct H₂ splitting between B and N atoms, without prior H₂ 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 H₂ with several lightly substituted (Z,Z,Z) COT molecules, with BR₂ and NR₂ at the C2 and C3 positions. The COT skeleton provides the possibility to introduce R¹ and R² substituents as well, so that one can stabilize the generated cation–anion pair (–NH₃⁺ and –BH₃⁻) to facilitate the reaction.

Fig. 10 shows the calculated reaction path. A24, the molecule with one BH₂ and one NH₂ group, originally has these groups conjugated (coplanar) with their respective double bonds. Please
recalling 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 $H_2$ coordinating mainly to the $BH_3$ substituent. However, the hydrogen molecule does not coordinate to the borane center in the absence of the $-NH_2$ group (i.e., $R^2 = BH_3$, $R^1 = H$). Thus, even though intermediate $A24 \cdot H_2$ looks to be boron-coordinated, the adjacent $NH_2$ group is essential. The coordinated hydrogen molecule is slightly stretched, to 0.79 Å. From there the reaction proceeds through $TS24$ (the $H \cdot H$ bond is stretched to 0.99 Å), only 7 kcal/mole higher at +21 kcal/mol, then on to product $A24 \cdot H^+ \cdot H^-$. 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. $\Delta E$ and $\Delta G$ 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 also a bond-shift process, single bonds converted into double bonds and vice versa, and that some dihedral angles (and with them steric encumberment 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 $\pi$-donors or $\pi$-acceptors. This could bring the energy of the B form down (for instance with –CN at positions 1, 2, and –NH$_2$ 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 stereoechemical constraints operative in the COT skeleton, we found an ideal path for potentially reversible $H_2$ activation in some amino- and borane-substituted COTs.

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