

Using Molecular Strain and Aromaticity To Create Ultraweak C–H Bonds and Stabilized Carbon-Centered Radicals

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Abstract: An approach based on relief of molecular strain in the parent hydrocarbon, extended conjugation in the radical, and the driving force toward aromaticity is used to design molecules with ultraweak C–H bonds. The molecular strain is generated by two fused rings containing (5,5)-, (5,6)-, or (6,6)-membered ring structures. Homodesmotic reactions are used to calculate the molecular strain enthalpy (MSE) of the parent hydrocarbons and the corresponding radicals, and to analyze how it changes through these reactions. B3LYP calculations are used to obtain the bond dissociation enthalpies (BDEs) for breaking one or more C–H bonds as well as the C–O bond formed after oxygen addition to the radical. Loss of a second H-atom can lead to very low R–H BDE values, especially when the ultimate product is aromatic. Molecular structures based on these ideas may be of interest as novel antioxidants based on carbon-centered radicals.

Introduction

Several research groups have recently analyzed the formation of carbon-centered radicals from their parent hydrocarbons R–H and have shown how such hydrocarbons can be used to design novel antioxidants.^{1–4} They identified several factors that led to increased stability, including (i) benzylic resonance stabilization, (ii) unpaired spin delocalization onto oxygen or other (unreactive) heteroatom, (iii) stereoelectronic effects, (iv) electron-withdrawing effects, and (v) steric effects. These effects are primarily focused on stabilization of the carbon-centered radical, with resulting weakening of the C–H bond. We have studied the relative contributions of these and other categories in previous work by the present authors,⁵ for a large number of examples. Using the same methodology, in this Article, we calculate gas-phase R–H and R–OO• bond dissociation enthalpies (BDEs) for a new series of molecules. We analyze the origin of the bond weakening effect and take advantage of a rather neglected structural feature, that is, molecular strain in the parent molecule and the oxygen adduct. We then use this theme, as well as the driving force toward aromatization, to explore a series of hydrocarbons containing fused rings. Some of these proposed compounds have low first and very low second C–H BDEs, forming stable products.

The term “molecular strain” is frequently used in discussing geometries and reactions of small molecules such as cyclopropane and cyclobutane, where the hybrid orbitals do not point along the carbon–carbon bonds, or in structures where the C–H bond orbitals are forced to be eclipsed. A few studies have focused on estimating its origin and magnitude. In early work, Wiberg⁶ discussed the origins of strain and provided a quantitative analysis of each source. Other relevant approaches can be found in works of Nicolaides et al.,⁷ Bond,⁸ and Rogers et al.,⁹ who have compared different theoretical methods for calculation of heats of formation and hydrogenation of olefins. Peck et al.¹⁰ have performed similar studies on benzenoid aromatics. In general, most of these methods derive strain energies by comparison between calculated heats of formation of the strained molecules versus the nonstrained congeners.

To provide a basis for comparison, we briefly summarize the magnitude of the effects of different categories of functional groups from previous work by Wright and Shadnia.⁵ We found that hyperconjugation effects, for example, as in (CH₃)₃C–H, lower the R–H BDE by up to 11 kcal/mol relative to the methyl radical, but have only a minor effect on the R–OO• BDE. Electron-withdrawing groups, particularly nitro and cyano, decrease the R–H BDE by up to 10 kcal/mol and the R–OO• BDE by up to 15 kcal/

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mol. Lone pair donors can also lower the R–H BDE by up to 13 kcal/mol, the strongest effect being seen for the amino group. Conjugative delocalization effects are more powerful and can lower the R–H BDE by up to a full 36 kcal/mol, and also decrease the R–OO• BDE by a maximum of 25 kcal/mol, for example, for trivinylmethane. Benzylic resonance stabilization also is very effective and can decrease the R–H BDE by up to 26 kcal/mol and the R–OO• BDE by up to 23 kcal/mol, as in triphenylmethane. Finally, captodative effects, which were not treated by Scaiano et al.,¹ show some of the largest bond-weakening effects, up to a maximum of 35 and 28 kcal/mol for R–H and R–OO•, respectively. Note that it was not always possible to separate these effects from one another and that molecules containing multiple functional groups do not necessarily act additively. However, this brief summary provides a reference standard against which any novel bond-weakening effects can be compared.

Method of Calculation

A density functional approach using the B3LYP functional with small (6-31G(d)) and large (6-311+G(2d,2p)) basis sets, termed the Medium-Level Model 3 (MLM3) method, was defined previously.^{5,11} Briefly, geometries and frequencies are obtained using B3LYP/Small, with a correction factor of 0.98 for frequencies. Single-point energies at the computed minimum are obtained using B3LYP/Large for closed shells, or the restricted open-shell specification ROB3LYP/Large for open-shell radicals. A correction factor of +2.0 kcal/mol is added to the (absolute) enthalpy of doublet radicals, whereas no correction factor is used for triplet states (e.g., the oxygen molecule) or the hydrogen atom. This method gave gas-phase R–H and R–OO• BDEs to within 2 kcal/mol where experimental data were available for comparison. This is sufficiently accurate to make discussion of BDEs and radical stability meaningful.

Most structural features including conjugation and electronic effects are well treated using B3LYP.^{5,12} For highly strained hydrocarbons, however, the method has been demonstrated to underestimate the magnitude of molecular strain energies. For example, Walker et al.¹³ used homodesmotic reactions (HDRs) and several theoretical techniques to calculate molecular strain energies for a variety of highly strained hydrocarbons. Actual measurements are usually in terms of enthalpies, so we can define the molecular strain enthalpy (MSE) for cyclopropane as the enthalpy change for the reaction cyclopropane + 3CH₃CH₃ → 3CH₃CH₂CH₃ where the HDR matches hybridization types (all sp³) and C–H substitution patterns (e.g., 3CH₂ groups for reactants and products, 6CH₃ groups each). The same approach can be used to define the HDR for a radical; for example, for the cyclopropyl radical the appropriate HDR would be cyclopropyl• + 3CH₃CH₃ → CH₃CH•CH₃ + 2CH₃CH₂CH₃.

In the next section, we investigate the discrepancy between the molecular strain enthalpy (MSE) as calculated by Walker et al.¹³ using the more accurate G1 method with that obtained using B3LYP (their calculations and ours). For this discussion, we use their set of highly strained hydrocarbons. It will be shown that the MSE values obtained with B3LYP can be

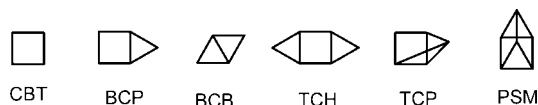


Figure 1. A subset of structures used from the data set of Walker et al.

Table 1. Calculation of Molecular Strain Enthalpy, Defined as the Enthalpy Change, ΔH_{298}° (g), for Homodesmotic Reactions Involving Structures Shown in the First Column (See Figure 1)^a

structure	MSE (Walker et al. ¹³)		MSE (this work)
	G1	B3LYP ^b	B3LYP ^c
CBT	26.0	22.7	23.9
BCP	55.4	46.1	48.4
BCB	66.8	55.7	58.7
TCH	81.5	66.8	70.5
TCP	106.2	90.2	94.2
PSM	143.4	121.7	126.9

^a All units are in kcal/mol. ^b Small basis = 6-311G(d,p); large basis = 6-311+G(3df,2p); unrestricted open-shell method. ^c Small basis = 6-31G(d); large basis = 6-311+G(2d,2p); restricted open-shell method.

adjusted, so that use of B3LYP methodology becomes as accurate as G1, no matter how highly strained the system.

Results and Discussion

A. Correction of B3LYP Values for Strained Systems.

A subset of the structures used by Walker et al. is shown in Figure 1. The subset was chosen so as to span the range of values of MSEs in approximately equal increments. These highly strained hydrocarbons show a combination of ring strain and steric strain, the latter caused by eclipsing of C–H bond orbitals. Table 1 shows the molecular strain enthalpy (MSE) obtained for the homodesmotic reaction for each structure, using G1 and B3LYP calculations of Walker, along with our own B3LYP calculation done with the MLM3 method.

As shown in Table 1, MSEs for these compounds (using G1 values) range from the moderately strained cyclobutane (26 kcal/mol) to the very highly strained prismane (143 kcal/mol); this should be sufficient to show any defects in the B3LYP methodology. Comparing B3LYP implementations, our own B3LYP protocol is closer to G1 and is therefore preferable, although both are significantly underestimating the MSE for the more highly strained systems.

Figure 2 shows a plot of our B3LYP values of the MSE versus the G1 values of Walker. There is a near-perfect linear fit with $R^2 = 0.9995$ for the equation:

$$\text{MSE(B3LYP)} = -0.0288 + 0.8821\text{MSE(G1)} \quad (1)$$

Inverting this equation gives

$$\text{MSE(G1)} = +0.0326 + 1.1338\text{MSE(B3LYP)} \quad (2)$$

Thus, the B3LYP method does indeed underestimate the MSE, by about 12%. However, this can be corrected for. Using the above equation, a corrected value for MSE(B3LYP) is equivalent to setting it equal to MSE(G1), which is determined from eq 2. Denoting the corrected value

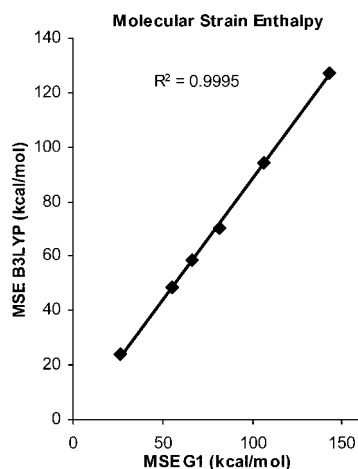


Figure 2. Molecular strain enthalpy (MSE) for B3LYP (our calculation) versus G1 (from Walker et al.).

Table 2. Comparison of the R–H BDE Values Calculated Using B3LYP (Our Work) versus G1 (Walker et al.)^a

structure	G1		B3LYP		
	BDE	BDE	MSE (parent)	MSE (radical)	BDE*
CBT	100.5	98.5	23.9	25.6	98.8
BCP	100.1	99.0	48.4	50.5	99.3
BCB	101.1	100.4	58.7	62.3	100.9
TCP	103.6	102.9	94.2	100.2	103.6
TCP	113.4	112.6	94.2	112.1	114.9
PSM	107.9	106.9	126.9	139.1	108.5

^a For the structure codes, see Figure 1. BDE* is the corrected B3LYP value for BDE. All values are in kcal/mol.

as $\text{MSE}(\text{B3LYP}^*)$, the correction factor is $\Delta = \text{MSE}(\text{B3LYP}^*) - \text{MSE}(\text{B3LYP})$. Because Δ is positive, adding Δ to the absolute enthalpy of the strained system effectively corrects for the B3LYP underestimate.

We have repeated this correlation for radicals using HDRs and obtained the same correlation parameters as those given above (data not shown). Thus, to obtain a BDE, for example, for $\text{R-H} \rightarrow \text{R}^* + \text{H}^*$, the MSE is calculated for parent and radical independently. Absolute enthalpy values H°_{298} are corrected for each, and the (gas-phase) BDE is the enthalpy change for the dissociation reaction.

It is also important to mention that because the magnitudes of MSE for the parent molecule and its radical are often very similar, the B3LYP error on absolute enthalpies of these species is canceled out in calculation of BDE values. Thus, as shown in Table 2 for the structures of Figure 1, even though these structures contain significant amounts of strain ($\text{MSE} = 25\text{--}145$ kcal/mol), the difference in MSE of parent and radical is much smaller (2–20 kcal/mol). This leads to the corrected BDE values (BDE^*), which differ by no more than 2.6 kcal/mol from the uncorrected BDE values.

B. BDE Values for Fused Ring Systems. Figure 3 shows the ring structures of interest in this Article. Many of these structures have two exchangeable hydrogen atoms. Because they can form intermediate radicals, oxygen adducts, and second dissociation products, a reaction scheme showing the various possibilities is given in Figure 4.

Structures **A1** and **A2**, also shown in Figure 5a, are two forms of pentadiene, that is, the conjugated 1,3-pentadiene

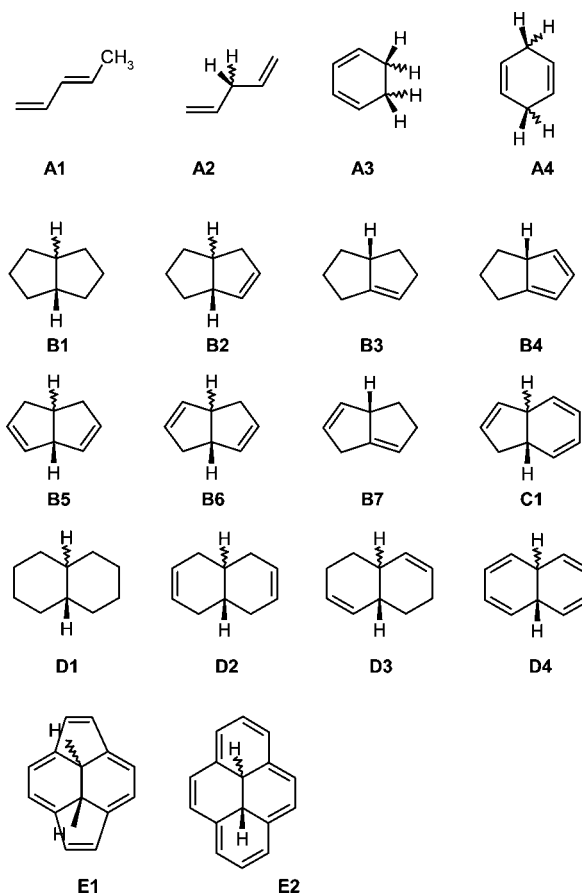


Figure 3. Molecular structures.

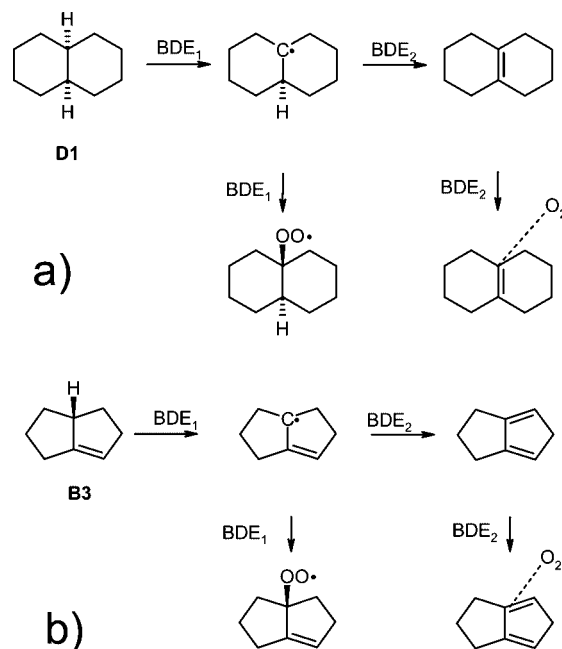


Figure 4. Reactivity scheme. (a) *trans*-**D1** (two exchangeable hydrogen atoms at ring junction), (b) **B3** (second exchangeable H-atom from ring).

and the “skipped diene” 1,4-pentadiene. **A3** and **A4** are the equivalent cyclic structures 1,3-cyclohexadiene and 1,4-cyclohexadiene, respectively. **B1–B7** are formed from the fusion of two cyclopentane rings, denoted (5,5), and contain variable amounts of unsaturation. Structures **B1**, **B2**, **B5**, and

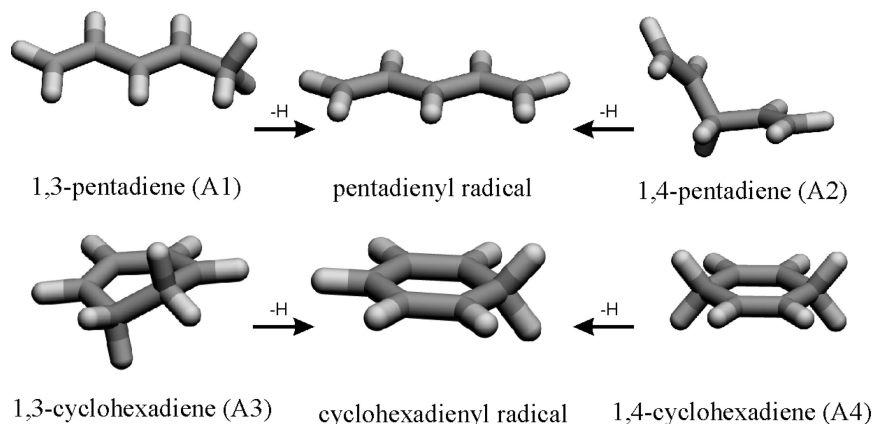


Figure 5. (a) Structures of the pentadienes and their radical; and (b) structures of cyclohexadienes and their radical.

B6 can have *cis*- or *trans*-dihydrogen stereochemistry at the central bond. **C1** is the (5,6) ring combination, whereas **D1–D4** are the (6,6) combinations. Finally, **E1** and **E2** are two additional multiring structures.

The MLM3 method was used to calculate gas-phase BDEs for loss of the first H-atom from R–H, denoted R–H BDE₁, and for loss of oxygen after addition to the corresponding radical R*, denoted R–OO* BDE₁. For most of the compounds discussed in this Article, there is an additional weak C–H bond present in the initial carbon radical. Loss of the second H-atom from R* is denoted R–H BDE₂. Similarly, loss of oxygen after addition to the product of this step is denoted R–OO* BDE₂.

The products of the second hydrogen abstraction are closed-shell molecules. In one-half of the cases, addition of oxygen to such molecules results in high-energy molecules, which are nevertheless trapped in a potential minimum. High energies of such adducts are reflected in positive enthalpy changes for the addition reaction, and correspondingly negative BDE values. These high-energy complexes are nevertheless bound by long C–O bonds but must overcome an energy barrier to separate. In other cases, mostly for structures that are less crowded around the radical center, energy minimization gradually increases the C–O bond distance beyond the limits for a covalent bond and results in structures in which oxygen lies in a shallow van der Waals minimum relative to the parent compound. This weak van der Waals interaction results in small positive BDE values in the range of 1–4 kcal/mol. Such cases are identified with an asterisk in Table 3. For all compounds, the four calculated BDE values are given in Table 3.

Corrected values of the R–H BDEs were obtained by applying the correction factor Δ to the parent compound, and a second value of Δ for the radical. The appropriate homodesmotic reactions are given in the Supporting Information. Both corrected (BDE*) and uncorrected R–H BDEs are given in Table 3. No correction factors were determined for oxygen addition reactions. The table also contains a column labeled strain release enthalpy (SRE). This is the difference in (corrected) molecular strain enthalpy between the radical R* and its parent hydrocarbon R–H. The sign follows the convention for enthalpy change, so when the SRE is negative the parent is more strained than the radical.

Table 3. BDE Values of Compounds in Figure 3^a

structure	R–H				R–OO*			
	BDE ₁	SRE	BDE ₁ *	BDE ₂	SRE	BDE ₂ *	BDE ₁	BDE ₂
A1	82.7						11.9	
A2	74.1						6.5	
A3	75.2			23.4			8.7	2.4*
A4	75.4			23.4			8.7	2.4*
<i>cis</i> - B1	94.9	−0.3	94.8	36.2	−5.3	35.4	32.8	−23.4
<i>trans</i> - B1	85.0	−9.1	83.6	39.0	−2.9	38.6	30.9	−19.3
<i>cis</i> - B2	87.2	9.4	88.5	44.4	2.9	44.8	24.0	−15.7
<i>trans</i> - B2	74.8	−12.4	73.0	44.4	2.9	44.8	−10.4	−15.7
B3	81.9	−2.0	81.6	46.8	32.0	51.4	18.6	−15.8
B4	77.2	2.6	76.9	52.1			6.2	2.5*
<i>cis</i> - B5	81.0	3.9	81.5	50.2	8.5	51.4	16.5	−10.9
<i>trans</i> - B5	63.4	−11.5	61.7	50.2	8.5	51.4	−15.6	−10.9
<i>cis</i> - B6	90.2	12.8	92.0	40.1	27.9	44.1	5.8	−19.4
<i>trans</i> - B6	65.9	−29.9	61.6	45.9	38.2	51.5	−0.1	−19.4
B7	73.5	−4.3	72.8	51.3	−0.8	51.2	9.5	−12.9
<i>cis</i> - C1	69.1	3.8	69.7	26.5			1.1	2.4*
<i>trans</i> - C1	61.8	−2.6	61.5	23.0			−5.7	3.2*
<i>cis</i> - D1	95.4	1.6	95.6	32.7	8.9	34.0	32.3	−28.7
<i>trans</i> - D1	96.0	2.2	96.3	35.6	11.4	37.3	8.1	−28.7
<i>cis</i> - D2	87.0	−6.4	86.1	31.5	0.6	31.6	−23.9	3.4*
<i>trans</i> - D2	95.3	0.9	95.2	31.5	0.6	31.6	−23.9	3.4*
<i>cis</i> - D3	81.2	−1.7	81.7	44.6			16.7	−16.2
<i>trans</i> - D3	80.1	−2.7	79.7	44.4			15.6	−15.3
<i>cis</i> - D4	60.2	−6.3	59.3	6.8			−4.7	2.6*
<i>trans</i> - D4	60.5	−6.0	59.7	6.8			−4.6	2.6*
<i>cis</i> - E1	79.1			9.0			6.2	2.5*
<i>trans</i> - E1	57.7			25.5			−9.3	1.9*
<i>cis</i> - E2	56.0			10.3			−13.2	3.8*
<i>trans</i> - E2	46.9			10.3			−13.2	3.8*

^a All values in kcal/mol. SRE is the corrected strain release enthalpy, and BDE₁* and BDE₂* are the corrected values of BDE₁ and BDE₂.

We found the data in Table 3 for structures **A1–A4** to give a surprising result, and further analysis led to development of the main theme of this Article. Thus, the conjugated pentadiene **A1** and the skipped diene **A2** give rise to the same pentadienyl radical; see Figure 5a. Because of 4-center conjugation, the parent hydrocarbon **A1** is more stable than **A2**, which has two isolated double bonds, so **A1** should have the larger R–H BDE₁. As expected, the BDE₁ values of 82.7 and 74.1 kcal/mol for **A1** and **A2**, respectively, reflect this difference in stability of the parent molecule. Note that **A2** is very nonplanar, due to the sp³ hybridization at the central carbon, thus minimizing any interaction of the isolated π -systems via hyperconjugation through the center methylene group. For the analogous cyclic compounds, both 1,3-cyclohexadiene (**A3**) and 1,4-cyclohexadiene (**A4**) give rise

to the same cyclohexadienyl radical (Figure 5b) and would be expected to follow the above trend in R–H BDE₁. However, their BDEs are essentially identical at 75.3 ± 0.1 kcal/mol.

Why is the cyclic system so different from the straight chains? The carbon skeleton of the cyclohexadienyl radical is planar, as is the 1,4-cyclohexadiene **A4** (Figure 5b). However, the carbon skeleton of 1,3-cyclohexadiene, **A3**, is twisted out of plane by 8° . The adjacent methylene groups show a dihedral angle H–C–C–H of 27° instead of the optimal 60° (in cyclohexane). The resulting steric strain caused by adjacent bond pair repulsions destabilizes **A3**, causing an out-of-plane twist for the conjugated group, partially neutralizing its 4-center conjugation, and giving (coincidentally) the same absolute enthalpy for both **A3** and **A4**.

Loss of a second H-atom from the cyclohexadienyl radical formed in **A3** and **A4** converts the molecule into the closed-shell aromatic benzene ring, so there should be a strong driving force, as reflected in a low value for R–H BDE₂. This is certainly the case, with the remarkably low value of 23.4 kcal/mol for both **A3** and **A4** (the intermediate carbon radical has the same structure for each). The R–H BDE₂ for both **A3** and **A4** is so low that they should transfer the H-atom to any available radical whose BDE for forming the parent molecule is greater than 23.4 kcal/mol, that is, to almost anything. Thus, at the same time the target radical is deactivated by H-atom transfer, the cyclohexadienyl radical will be converted into the highly stable closed-shell molecule benzene.

Next, consider the tendency of molecular oxygen to add to the carbon radical R• to form R–OO•. For comparison, methane has an R–H BDE of 106.1 and an R–OO• BDE of 32.0 kcal/mol.⁵ To prevent oxygen addition, we need to weaken the R–OO• bond as much as possible. We showed previously⁵ that there is a good correlation between the R–H and R–OO• BDEs, given by $\text{R–OO• BDE} = -67.2 + 0.95 \text{ R–H BDE}$, with correlation coefficient $R^2 = 0.925$. Therefore, in general, molecules with weaker R–H bonds lead to radicals that form weaker R–OO• bonds, that is, are more resistant to oxygen addition. Structures **A1–A4** show this characteristic weakening of the R–OO• bond as the R–H bond gets weaker. When the second H-atom is lost from **A3** or **A4**, and benzene is formed, molecular oxygen does not form a covalent bond to benzene but forms a weakly bound van der Waals complex. Table 3 shows that the binding energy is only 2.4 kcal/mol, consistent with a van der Waals complex.

Compounds **B1–B7** introduce molecular strain into parent R–H and oxygen adduct. Figure 6 shows the parent compound bicyclopentane, **B1**, in both its trans and cis isomers. Clearly, the trans-parent compound is more strained, because its BDE₁ is ca. 11.2 kcal/mol smaller than that for the cis-compound (83.6 vs 94.8 kcal/mol, respectively). Note that where cis and trans isomers are possible, as in **B1**, the R–H BDE₂ can be different, in this case 35.4 versus 38.6 kcal/mol for cis and trans, respectively. The structures of the cis- and trans-radicals are different, and because our optimization procedure begins with the parent compounds,

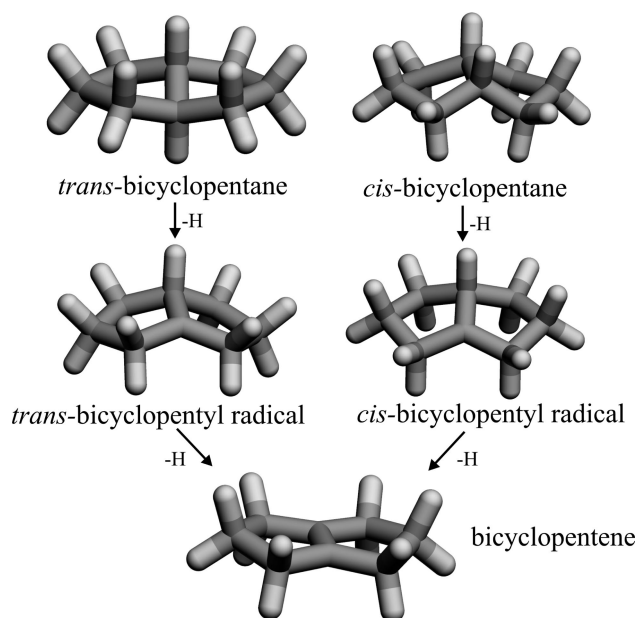


Figure 6. Optimized geometries of bicyclopentanes (*cis*-**B1** and *trans*-**B1**), their radicals, and the ultimate product, bicyclopentene.

different local minima result, which we believe cannot be easily interconverted.

Compounds **B2–B7** continue this theme, introducing additional stabilization to the radical by allowing for allylic (**B2**, **B3**, **B6**) or pentadienylic (**B4**, **B5**, **B7**) conjugation. For the allylic case, this causes R–H BDE₁ to drop by 6–10 kcal/mol (compare **B2** vs **B1**) with an equivalent drop in R–OO• BDE₁. The pentadienylic case is even more dramatic, where for example in *trans*-**B5** the R–H BDE₁ has dropped to a very low 61.7 kcal/mol.

Using only one double bond in *cis*-**B2** and *trans*-**B2** affects the first hydrogen abstraction and reduces R–H BDE₁ to fall within a favorable range (73.0 kcal/mol for *trans*-**B2**) for an antioxidant.¹⁴ Also, the R–OO• BDE₁ in these compounds has decreased substantially in comparison with **B1**. The *trans*-**B2** compound has negative values for dissociation of oxygen in the first or second step and is therefore resistant to oxygen addition. By moving the position of the double bond, the parent molecule in **B3** is more planar than *trans*-**B2** so the strain release enthalpy for this compound (SRE = -2.0 kcal/mol) falls between those of the *cis*- and *trans*-**B2**. Clearly, the BDE₁ values follow the trend ($88.5 > 81.6 > 73.0$).

Placing two double bonds on the same ring in **B4** reduces the R–H BDE₁ even further because the radical is stabilized by pentadienylic conjugation. At the same time, because the planar side of the structure (the cyclopentadiene ring) does not interfere with the nonplanar side (cyclopentane), the molecular strain in this structure is diminished, as confirmed by SRE = 2.6 kcal/mol.

Placing both double bonds on different rings in **B5** gives the skipped diene conjugation similar to **A2**. The difference from the strain-free **A2** is that the two isomers of **B5** release different amounts of strain through the hydrogen abstraction reaction (SRE = 3.9 and -11.5 kcal for the *cis*- and *trans*-**B5**, respectively), predictably changing the BDE₁ values from

75.2 kcal/mol for **A2** to $75.2 + (3.9) = 79.1$ (ca. 81.5 kcal/mol) for the cis and $75.2 + (-11.5) = 63.6$ (ca. 61.7 kcal/mol) for the trans isomer.

When placing two double bonds adjacent to either active hydrogen in *cis*-**B6** and *trans*-**B6**, the conjugative stabilization effect is divided among both first and second hydrogen abstractions. At the same time, in the trans isomer the two cyclopentene rings are highly twisted due to the opposite location of the double bonds, because the structure tends to become planar on the sp^2 centers and nonplanar on the sp^3 centers. Thus, the *trans*-**B6** compound shows the highest amount of strain release enthalpy ($SRE = -29.9$ kcal/mol), leading to a low BDE_1 of 61.6 kcal/mol. Overall, *trans*-**B6** shows low R–H BDE values and negative BDEs for both oxygen adducts, which makes it another potentially interesting antioxidant. The compound **B7** uses the same skipped diene system as **B5**, with the difference that the double bonds in **B7** give both rings a quasi-planar conformation, which have very little strain, resulting in a small amount of strain release ($SRE = -4.3$ kcal/mol).

Overall, the calculated SRE values reveal that the trans conformations of (5,5)-membered ring structures in general show considerable strain release ($SRE = -9$ to -29 kcal/mol), which causes the lowering of R–H BDE_1 values, while the cis conformations show only slight to moderate strain release ($SRE = -0.3$ to $+12.8$ kcal/mol) for the first hydrogen abstraction. The variations of the SRE and BDE values reveal that while it is relatively easy to induce molecular strain into a structure, it is difficult to cause it to be released in a hydrogen abstraction reaction. The results also reveal that the position of double bonds and ring fusions needs to be designed properly to give maximum molecular strain for the parents while giving increased conjugation and lower molecular strain for the radical.

Fusing a 5- and 6-membered ring, as in **C1**, allows an additional factor, aromaticity, to stabilize the final product. Now the indene ring can form, containing one benzene unit, so that both R–H BDE_1 and R–H BDE_2 are very low for **C1**, in both cis and trans configurations (69.7, 26.5 vs 61.5, 23.0 kcal/mol, respectively). From the SRE values (3.8, -2.6 kcal/mol for the cis and the trans isomers, respectively), it is clear that these structures undergo only slight changes in molecular strain through the hydrogen abstraction reaction.

This trend can be continued with fusion of two 6-membered rings, as in **D1–D4**. The two isomers of **D1** are almost strain-free ($SRE = 1.6, 2.2$ kcal/mol for cis and trans, respectively) for the abstraction of the first hydrogen. **D2** is similar to **D1** because the double bonds are not conjugated with the central bond. The double bonds in *cis*-**D2** cause a small amount of molecular strain that is released by hydrogen abstraction ($SRE = -6.4$ kcal/mol), lowering its R–H BDE_1 to 86.1 kcal/mol. **D4** is particularly interesting because in both cis and trans configurations BDE_1 is very low (ca. 59 kcal/mol), and BDE_2 is only 6.8 kcal/mol; that is, after the first dissociation the second H-atom is almost unbound. The SRE values ($-6.3, -6.0$ kcal/mol for *cis*-**D4** and *trans*-**B4**, respectively) reveal that there is no significant amount of strain release for the abstraction of first hydrogen. Thus, the major driving force is the extended conjugation. For the

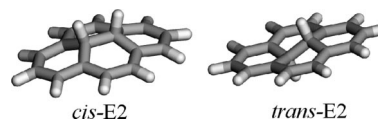


Figure 7. Compounds *cis*-**E2** and *trans*-**E2**.

second step, the driving force is aromatization, forming the product naphthalene.

In general, SRE values reveal that the (5,6)- or (6,6)-membered ring systems are not as useful as the (5,5)-membered ring for taking advantage of molecular strain in lowering R–H BDE values. They can, however, take advantage of conjugation and aromaticity to yield very low R–H BDE values.

An extreme form of this approach to weakening the C–H bond would be *trans*-**E1**, a (6,6,5,5) fragment of a buckyball, where its R–H BDE_1 has dropped to ca. 58 kcal/mol. One could imagine a buckyball that has been modified to include a local single bond, as in **E1**. In that case, the weakening of the C–H bond should be even more extreme.

As a final example consider **E2**, with its (6,6,6,6) structure. As in **D4** and **E1**, the periphery of the parent molecule is fully conjugated, but the molecule is not aromatic (Figure 7). Now the R–H BDE_1 has dropped to 46.9 kcal/mol for the trans isomer, the lowest value in Table 3.

We conclude this discussion with some observations on trends in Table 3. Similar to the comparison made in Table 2, comparison of the values for BDE_1 and the corrected values BDE_1^* shows very little difference between the two. Approximately one-half of the entries release strain, whereas the other half increase it; the magnitude of the correction never exceeds ca. 4 kcal/mol and is usually less than 2 kcal/mol. This means that uncorrected values of B3LYP energetics could have been used for these calculations with relatively little error. In general, this also applies to BDE_2 values, although there is one case where the deviation is as large as 6 kcal/mol. The significant amounts of strain introduced into the parent molecule in the trans geometry mean that these structures are “strain traps”, which is the cause of their low BDE values.

Relevance to Experimental Work

Ferjančić et al.¹⁵ studied free radical additions to strained cycloalkenes and concluded that the strain relief in the intermediate radical accelerates the addition reaction. The reactions we studied in this work do not involve high energy transition states as those of the Ferjančić study, but they do involve strain relief (in hydrogen abstraction reactions) or gain (in oxygen addition reactions). Thus, it is possible that the strain affects the kinetics of these reactions favorably. This is particularly interesting, because antioxidants that generate carbon radicals are known to have slower reaction rates than those that generate oxygen-centered radicals.

Regarding more highly conjugated compounds, Small et al.¹⁶ have studied the ultraweak σ -bond formed in dimerization of phenalenyl radical and estimated the BDE of this C–C bond to be about 16 kcal/mol. Our calculations show that similar to radicals formed by **E1** and **E2**, the weak C–H bond in phenalenyl radical is the result of increased conjugation.

tion and relief of strain for radical formation. While the phenalenyl radical tends to self-associate and form a dimer, it has been shown¹⁷ that by using appropriately bulky functional groups, a persistent radical can be isolated and even crystallized. A similar steric approach can be used to inhibit the possible dimerization reactions of our about-to-be formed aromatic compounds such as **E1** and **E2**. This approach has been exploited to generate a continuous source of radicals for use as chain-breaking antioxidants.¹⁸

Verevkin et al.¹⁹ found the compound *cis*-**D4** to be the “thermodynamic sink” (the most stable) of all interconversions of (CH)₁₀ compounds. Because they only confined their search to experimentally discovered compounds, the trans compound was not considered. According to our calculation, the trans conformer is 0.3 kcal/mol more stable.

Antioxidant Design

Antioxidants that form carbon-centered radicals by abstraction from a C–H bond are limited in usefulness because they react more slowly than antioxidants based on abstraction from an O–H bond.²⁰ However, as the R–H BDE drops drastically, these kinetic differences should be reduced. There is an interesting point of comparison with phenolic antioxidants. Phenols are often metabolized biologically to catechols and hydroquinones. These are good H-atom donors and oxidize first to the semiquinone and ultimately to the quinone. Reducing agents such as ascorbate or glutathione are often required to send the reactive semiquinones back to parent catechols (or hydroquinones), or else the very electrophilic quinones can act as tumor initiators by alkylating DNA.²¹ When reducing agents are present, the catechol (or phenol) acts as a catalytic antioxidant because the parent compound is regenerated from the reducing power in the cell. However, when oxidation (often autooxidation) exceeds reduction of the oxy-radical, the cell enters into a state of oxidative stress, usually with negative consequences for the organism.

Now consider antioxidants based on carbon-centered radicals as described in Table 3. The first BDE is low, so reaction with a target radical such as peroxy should be relatively fast. The second BDE is very low, so the reaction will quickly go to completion, forming the relatively stable olefin product. Because olefins are much less electrophilic than quinones, they should pose much less of a tendency to cause oxidative stress. Once formed, the olefin is unlikely to be reduced. Such an antioxidant is then acting in a stoichiometric rather than in a catalytic mode. This will require restoring the supply of starting material. However, due to the presence of two exchangeable H-atoms, the parent compound is acting as a bivalent donor antioxidant. This is an improvement over a monovalent antioxidant. One could continue this theme by designing structures that are polyvalent donors with multiple weak C–H bonds.

Conclusions

Molecular strain and conjugation effects can be effectively used to design structures that produce carbon-centered radicals. Classical substituent effects that stabilize the radical center can be used in combination with molecular strain to

design molecules with ultraweak C–H bonds. One possible strategy is to design structural motifs suitable for the quasi-planar orientation of bonds on the radical center, so that the tetrahedral orientation of bonds in the parent and oxygen adduct will be strained. Some simple examples of compounds following this theme were demonstrated, including (5,5)-, (5,6)-, (6,6)-membered fused rings.

Homodesmotic reactions were used to derive correction factors for the absolute enthalpy of both parent and radical. The corrected enthalpies were used to obtain the corrected values of the BDE and the strain release enthalpy (SRE). We demonstrated that this parameter (MSE) can be used to correct for the B3LYP error in highly strained molecules and to obtain BDE values that correspond closely to higher level calculations. The magnitude of this correction however was usually small. The SRE value reveals how much the molecular strain that is engineered in the parent molecules is released through a hydrogen abstraction reaction. The SRE values reveal that the trans isomers of (5,5)-membered systems are ideal “strain traps”, which can lower the R–H BDE₁ values by up to 30 kcal/mol.

The fused-ring compounds can undergo subsequent hydrogen loss and show low first and especially low second R–H BDEs. At this stage, these compounds end up as stable closed-shell products, effectively terminating the propagation of oxidative chain reactions. While for classical carbon-centered radicals the reaction rates of C–H bond dissociation are slower than ideal for antioxidant activity, it is likely that the very weak C–H bonds of the parent molecules in our suggested compounds will increase these reaction rates considerably. This leads naturally to the idea of a stoichiometric, bivalent donor antioxidant generating nontoxic products.

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Supporting Information Available: Homodesmotic reactions used to calculate MSE values. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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