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The Effect of Carbonyl Substitution on the Strain Energy of Small Ring Compounds and Their Six-Member Ring Reference Compounds

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Abstract: High level ab initio calculations have been applied to the estimation of ring strain energies (SE) of a series of three- and six-member ring compounds. The SE of cyclohexane has been estimated to be 2.2 kcal/mol at the CBS-APNO level of theory. The SE of cyclopropane has been increased to 28.6 kcal/mol after correction for the one-half of the SE of cyclohexane. The SEs of a series of carbonyl-containing three-member ring compounds have been estimated at the CBS-Q level by their combination with cyclopropane to produce a six-member ring reference compound. The SEs of cyclopropanone (**5**), the simplest α-lactone (**6**) [oxiranone], and α-lactam (**7**) [aziridinone] have been predicted to be 49, 47, and 55 kcal/mol, respectively, after correction for the SE of the corresponding six-member ring reference compound. The SEs of cyclohexanone, δ-valerolactone, and δ-valerolactam have been estimated to be 4.3, 11.3, and 5.1 kcal/mol, respectively. Marked increases in the SE of silacyclopropane and siladioxirane have been established, while significant decreases in the SEs of phosphorus, sulfur, dioxa- and diaza-containing three-member ring compounds were observed. The ring strain energies of the hydrocarbons (but not heterocycles) exhibit a strong correlation with their C−H bond dissociation energies.

1. Introduction

The assessment of ring strain in small ring compounds remains a topic of major interest to the organic chemist.[1] An accurate estimate of the effect that ring strain has upon chemical reactivity and ground state energy can be a major asset to the synthetic chemist. Cyclopropane, the archetypal simplest strained carbocycle, has played a unique role in the history of ring strain and remains one of the standard structures to which other strained systems are compared. The conventional strain energy of cyclopropane was estimated initially to be 27.6 kcal/mol by Benson[2a] based upon well-established group equivalent methods.[3] However, the strain energy (SE) of cyclopropane has also been wedded to that of cyclohexane since its generally accepted SE can be derived from the experimental ΔH_f for cyclopropane (12.74 kcal/mol) and one-half of that of cyclohexane ($\Delta H_f = -29.43$ kcal/mol).[2b] The SE for cyclopropane, 27.46 kcal/mol, has recently become the more generally accepted experimentally derived strain energy (SE = 27.5 kcal/mol). Thus, these two cyclic hydrocarbons have been at the cornerstone of the estimation of SE for hydrocarbons for several decades. However, this experimentally derived SE for cyclopropane is based upon the assumption that cyclohexane is strain free (SE = 0.0 kcal/mol).

It is well established that the introduction of a trigonal or sp^2 carbon center into a three-member ring hydrocarbon has a considerable impact upon the strain energy of small ring alkenes.[4a] For example, the SE of methylenecyclopropane is estimated to be 40.9 kcal/mol, and the heat of formation of isomeric 1-methylcyclopropene is 10.2 kcal/mol higher.[4b] Initially, Wiberg[4a,b] measured the heats of formation of these two strained compounds and suggested that the introduction of each trigonal carbon center into a cyclopropane ring introduces an additional 12−14 kcal/mol of ring strain. Borden[5] has also suggested that the additional ring strain in methylenecyclopropane, relative to methylcyclopropane, is not totally the result of an increase in angular strain but also the *presence* of a very strong *tert*-C−H bond (106.5 kcal/mol) in methylcyclopropane and its *absence* in methylenecyclopropane. More recently, we have suggested that the increased SE of such small ring alkenes as methylenecyclopropane and 1-methylcyclopropene, relative to methylcyclopropane, can also be attributed to a decrease in their thermodynamic stability as a result of very low bond

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(1) For recent discussions of the methods for the calculation of ring strain energies, see: (a) Khoury, P. R.; Goddard, J. D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103. (b) Alcami, M.; Mo, O.; Yanez, M. *J. Comput. Chem.* **1998**, *19*, 1072 and references therein. (c) Cremer, D.; Kraka, E. In *Theoretical Models of the Chemical Bond*; Maksic, Z. B., Ed.; Springer: Heidelberg, 1990; Vol. 2, p 453. (d) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 4450.

(2) (a) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neil, H. E.; Rogers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279. (b) NIST *Standard Reference Database*, No. 69, June 2005 (http://webbook.nist.gov/chemistry.)

(3) For an excellent discussion of the various heat of formation group increments, see: Schleyer, P. v R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem.* **1970**, *92*, 2377.

(4) (a) Wiberg, K. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312. (b) Wiberg, K. W.; Fenoglio, R. A. *J. Am. Chem. Soc.* **1968**, *90*, 3395. (c) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Chemistry*; Wiley: New York, 1994; pp 676−678, 732.

(5) Johnson, W. T. G.; Borden, W. T. *J. Am. Chem. Soc.* **1997**, *119*, 5930.

10.1021/ja055086g CCC: $33.50

dissociation energies of allylic C−H bonds in these small ring alkenes.[6a]

It is now well accepted that the C−C and C−H bonds in cyclopropane are shorter than those in a more "normal" carbocycle, such as cyclohexane. It has also been recognized for some time that the C−H bonds of cyclopropane are stronger than those of cyclobutane or larger ring carbocycles and help to offset the increase in GS energy due to angle strain and weaker C−C bonds. The calculated C−C intrinsic bond energies (BE)[7] for cyclopropane, cyclobutane, and cyclohexane (73.2, 79.1, and 87.3 kcal/mol, respectively) are consistent with this concept. The long-standing controversy concerning the fact that three- and four-member ring hydrocarbons have comparable SE can now be readily rationalized; the greater C−C−C angular strain in cyclopropane is offset by its greatly increased C−H bond energies. We have recently put this suggestion on a quantitative basis with calculated C−H bond dissociation energies (BDE) at the G2, G3, and CBS-Q levels of theory.[6] The effect of relatively strong C−H bonds has been shown to be particularly important for cyclopropanes.[8] The C−H BDE in cyclopropane at 298 K has been measured to be 106.3 ± 0.3 kcal/mol, while the secondary C−H bond in propane is 98.6 ± 0.4 kcal/mol (ΔBDE = 7.7 kcal/mol). Ring strain energy is a delicate balance of stabilization and destabilization effects that manifest themselves in the "measured" strain energy of cyclic molecules.

Although the strain energy of cyclopropane has been extensively studied, far less emphasis has been place upon the SE of carbonyl-containing small ring compounds, such as cyclopropanone, α-lactones, and α-lactams. The question of the origin of the SE for these carbonyl-bearing cyclic compounds has received scant attention. Since the experimental estimates for the enthalpy of formation of cyclopropanone vary between ca. −3 and +5 kcal/mol, estimates of its strain energy have presented difficulties and only a single reliable source of its SE has been reported. Despite the paucity of experimental data, Williams et al.[9] have used ab initio calculations at the MP2 and QCISD(T) levels and experimental $\Delta H^\circ_{f,298}$ in a series of isodesmic reactions to estimate the SE of cyclopropanone to be 43 kcal/mol. He also suggested that the SE of the simplest α-lactone (oxiranone) was slightly less than that (40 kcal/mol). As we point out, in due course, these pioneering studies were remarkably accurate considering the level of theory that was available at that time.[9d]

We now extend our computational approach using the dimerization/combination protocol augmented with accurate C−H bond dissociation energies (BDE) to the estimation of strain energies in carbonyl-containing three-member ring compounds and related carbocycles and heterocycles. These combined data show quite convincingly that the thermodynamic stabilities of small ring hydrocarbons can be dramatically influenced by relative C−H BDE within a given ring size.

Table 1. Calculated C−H Bond Dissociation Energies (BDE = ΔH°_{298}, kcal/mol) at the G2, G3, CBS-Q, and CBS-APNO (in bold) Levels of Theory. Experimental BDEs are Given for a Comparison in the Last Column[a]

compound	G2	G3	CBS-Q **CBS-APNO**	expt.
ethylene	112.0	110.3	**111.1**	111.2 ± 0.8
cyclopropane	110.3	109.2	109.5, **109.5**	106.3 ± 0.3
methylcyclopropane ring C−H	110.5	109.4	109.5, **109.7**	
methylcyclopropane *tert*-C−H	107.6	106.5		
methylenecyclopropane ring C−H	99.3	97.6	96.5, **97.9**	
cyclobutane	101.9	100.6	100.9	96.5 ± 1.0
1-butene allylic C−H		84.2	83.1	
isobutylene methyl C−H	89.8		87.1, **89.2**	
methylenecyclobutane α-C−H		86.4	85.0	
methylenecyclobutane *β*-C−H		100.8		
cyclopentane	97.8	96.3	97.2	96.4 ± 0.6
cyclohexane	100.8	99.5	100.0	95.5 ± 1.0 99.3[b]
acetone α-carbonyl C−H bond		96.3	97.1, **96.7**	98.3 ± 1.8
cyclopropanone			**99.8**	
oxiranone (**6**)			**102.9**	
aziridinone (**7**)		100.3	**100.4**	
cyclobutanone α-C−H		93.7	94.0	
cyclobutanone *β*-C−H			101.5	

[a] *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed.; CRC Press LLC: Boca Raton, Florida, 2002. [b] Groves, J. T.; Han, Y.-Z. In *Cytochrome P450: Structure, Mechanism, and Biochemistry*, 2nd ed.; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1995; pp 3−48.

2. Computational Methods

Ab initio molecular orbital calculations[10] were performed with the GAUSSIAN 98 and G03 system of programs.[11] The reaction enthalpies and strain energies were calculated using G2, G3, CBS-Q, and CBS-APNO theory.[12] The G2 and CBS-Q methods are generally considered to be reliable to about 1.2 kcal/mol or less, and the G3 method is a slight improvement over these earlier methods. Perhaps the most accurate BDEs can be obtained, within this series, by the CBS-APNO[12] method despite its relative cost. In this procedure, geometries are optimized at the QCISD/6-311G(d,p) level with single point energy corrections at QCISD(T)/6-311++G(2df,p) with further energy corrections with an extrapolated basis set. Experimental heats of formation were taken from NIST.[2b] Homolytic bond energies (ΔE) quoted in the text are derived from total energies, while bond dissociation energies (BDE) are derived from ΔH°_{298}. Throughout the text, bond lengths are in angstroms and bond angles are in degrees. The energy values quoted in the text are at the G2, G3, CBS-Q, and CBS-APNO levels and are considered to be equally accurate for the purposes of discussion. A summary of the BDEs calculated by each of these methods is given in Table 1.

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(7) For a recent critical evaluation of the schemes used to calculate intrinsic bond energies (BE) leading to new estimates of the stabilization of cyclopropane due to C−H bond strengthening, see: Exner, K.; Schleyer, P. v. R. *J. Phys. Chem. A* **2001**, *105*, 3407.

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(9) (a) Rodriquez, C. F.; Williams, I. H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 953. (b) Ruggiero, G. D.; Williams, I. H. *J. Chem. Soc., Perkin Trans. 2* **2001**, 733. (c) Buchanan, G. J.; Charlton, M. H.; Mahon, M. F.; Robinson, J. J.; Ruggiero, G. D.; Williams, I. H. *J. Phys. Org. Chem.* **2002**, *15*, 642. (d) Using the same isodesmic equation and $\Delta H^\circ_{f,298}$ reported by Williams[9a,2b] (oxiranone + diethyl ether = oxirane + ethyl acetate), but with a more recent experimental heat of formation for oxiranone ($\Delta H^\circ_{f,298} = -47.3$ kcal/mol),[9e] we estimate an SE for oxiranone (based upon an SE for oxirane of 27.25 kcal/mol) of 39 kcal/mol, in excellent with earlier value suggested by Williams using the MP2/6-311G(d,p) method. (e) Schröder, D.; Goldberg, N.; Zurnmack, W.; Schwarz, H.; Poutsma, J. C.; Squires, R. R. *Int. J. Mass Spectrom. Ion Processes* **1997**, *165*/*166*, 71.

(10) (a) Frisch, M. J.; et al. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998; (b) *Gaussian 03*, revision B.05 (SGI64-G03RevB.05); Gaussian, Inc.: Pittsburgh, PA, 2003. See the Supporting Information for the full list of authors.

(11) (a) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214. (b) Schlegel, H. B. *Adv. Chem. Phys.* **1987**, *67*, 249. (c) Schlegel, H. B. In *Modern Electronic Structure Theory*; Yarkony, D. R., Ed.; World Scientific: Singapore, 1995; p 459.

(12) (a) Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221. (b) Curtiss, L. A.; Raghavachari, K.; Pople, J. A. *J. Chem. Phys.* **1997**, *106*, 1063. (c) Ochterski, J. W.; Petersson, G. A.; Montgomery, J. A. *J. Chem. Phys.* **1996**, *104*, 2598. (d) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764.

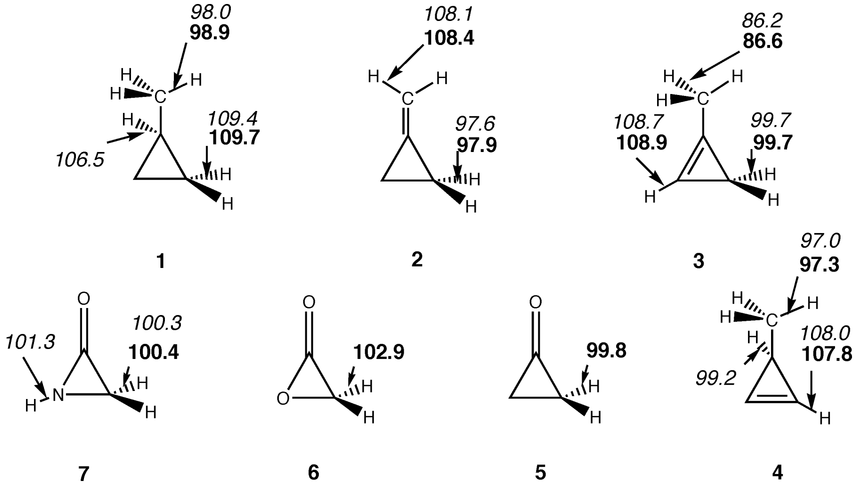

Figure 1. BDE (kcal/mol) calculated at G3 (italic) and CBS-APNO (bold) levels.

3. Results and Discussion

3.1. The Effect of Carbonyl Groups on C−H Bond Dissociation Energies. One variable that remains fairly constant, when determining the strain energy of three-member ring carbocycles, is angle strain. By definition, a typical three-member ring has bond angles of approximately 60°, yet the strain energy (SE) of a wide variety of three-member ring compounds exhibit SEs that can vary over a wide range up to 40 kcal/mol. Since Baeyer angle strain is dependent upon the force constant for bond angle distortion, the SEs for carbocycles and carbonyl-containing cyclic compounds can exhibit markedly different strain energies.[4c] This is especially true for cyclic ketones and lactones where the 120° normal sp^2 hybridized carbonyl carbon bond angle is essentially reduced by one-half in cyclopropanone. Thus, the Baeyer strain in cyclopropanone is not likely to be the same as that in cyclopropane. This may also be problematic for certain three-member ring heterocycles (e.g., Si), where the internal bond angles exhibit an even larger deviation.

We have established a definite correlation between the relative bond dissociation energies and the estimated SE in these strained molecules and now raise the question whether C−H BDEs also strongly impact the SE of small ring molecules that contain a carbonyl group. The origin of the presumably high strain energy of cyclopropanone remains an open question. At the outset of this study, we emphasize that although the determination of selected C−H BDEs is an integral part of our approach, by definition, the BDE derived in this manner does not necessarily represent the actual energy content of the bond in its molecular ground state.[13] The bond strength, which is usually evaluated in terms of its BDE, has two basic components: the intrinsic bond energy (BE) and the total (geometric and electronic) reorganization energy (R) of the two fragments arising from homolytic bond dissociation.[7] We have, however, in the past found an excellent *correlation* between C−H bond energies and strain energy, and it is this aspect of the BDE approach that we advocate.[6]

Wherever possible, we address the question of bond dissociation energies (BDE) in these relatively small molecules at the CBS-APNO level because the geometries are optimized at the QCISD/6-311G(d,p) level.[12] Consequently, the calculated energies should be within chemical accuracy (1−2 kcal/mol). The effect of the C−H BDE on the SE of related compounds becomes immediately obvious upon comparison of the bond strengths (Figure 1) of the ring C−H bonds (109.7 kcal/mol) of methylcyclopropane (**1**) to that of methylenecyclopropane (**2**) that are considerably lower (97.9 kcal/mol). A direct comparison of the SE of methylenecyclopropane and 1-methylcyclopropene (**3**, SE = 54.7 kcal/mol)[6a] is possible since these two isomeric cyclic hydrocarbons only differ by a vinylic versus a methyl group C−H bond. The greater strain energy for **3** (ΔSE = 15.2 kcal/mol)[6a] may be attributed, in part, to the three relatively weak allylic C−H bonds of the methyl group in **3** (97.3 kcal/mol). In contrast, only the two vinyl C−H bond energies of **2** (108.4 kcal/mol) are unusually strong and compare favorably to the analogous vinyl C−H bonds on ethylene (111.1 kcal/mol) and to the two vinyl C−H bonds (107.8 kcal/mol) of 3-methylcyclopropene (**4**). Isomeric cyclopropenes **3** and **4** have identical SE (54.7 and 54.8 kcal/mol),[6a] due in part to the cancellation of the homoallylic methyl C−H bonds in **4** (97.3 kcal/mol) and the ring hydrogens in **3** (99.7 kcal/mol).

The accepted SEs for methylenecyclopropane (40.9 kcal/mol) and cyclopropene (55.2 kcal/mol)[4] are typical of such highly strained molecules that have been the subject of much study. Far less emphasis has been placed upon the strain energy in the comparable carbonyl derivative, cyclopropanone, although it has usually been assumed to be quite high. The C−H bond energies in cyclopropanone (**5**) are only slightly greater than those in methylenecyclopropane. Calculation of the BDE in **5** presents considerable difficulty because upon homolytic C−H bond cleavage the ring opens at both the HF and DFT levels of theory. The C−H bond dissociation energies in the simplest lactone, oxiranone (**6**), or lactam, aziridinone (**7**), also do not rise to those in cyclopropane. Thus as we demonstrate below, inclusion of a carbonyl group within the three-member ring has an even greater impact upon the strain energy than insertion of

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(13) For approaches to calculate these two nonobservable contributors, BE and R, which are not directly measurable for molecules of this type, see: (a) Bader, R. F. W.; Tang, T.-H.; Tal, Y.; Biegler-Konig, F. W. *J. Am. Chem. Soc.* **1982**, *104*, 946. (b) Bader, R. F. W. *Atoms In Molecules: A Quantum Theory*; Oxford University Press: Oxford, 1990. (c) Grimme, S. *J. Am. Chem. Soc.* **1996**, *118*, 1529. (d) Krygowski, T. M.; Ciesielski, A.; Bird, C. W.; Kotschy, A. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 203. (e) Howard, S. T.; Cyranski, M. K.; Stolarczyk, L. Z. *J. Chem. Soc., Chem. Commun.* **2001**, 197.

a methylene group. The strain energy of these carbonyl-containing three-member rings is attributed largely to angular strain.

3.2. The Effect of Carbonyl Groups on Ring Strain Energy. Strain Energies Based upon Dimerization/Combination with Cyclopropane. One of the more useful methods to estimate the strain energy of small ring compounds was suggested by Liebman and his colleagues.[14] This relatively straightforward method is based upon the dimerization of a three-member ring compound to produce a six-member ring reference compound that *is presumed to be strain free*. We have used an extension of this protocol that involves the combination of the three-member ring with cyclopropane to produce a six-member ring reference compound.[6] For example, the dimerization of cyclopropane (Table 2, eq 1) affords a larger *ostensibly* strain-free molecule, cyclohexane, that differs only in the bond angles of the fragments and the number of its *gauche* interactions. On the basis of the differences in computed total energies, which include zero-point energy corrections, the dimerization of cyclopropane, where SE = $(2\ E_{\text{cyclopropane}} - E_{\text{cyclohexane}})/2$, gives an SE = 27.2 kcal/mol at the G2 level of theory,[6] and 27.8 and 27.3 kcal/mol at the CBS-Q and CBS-APNO levels, values in excellent agreement with the *conventional experimentally derived SE* (27.5 kcal/mol).[4a] To place the SE of this most celebrated carbocycle, cyclopropane, in perspective, combination of cyclopropene with cyclopropane (eq 2) affording cyclohexene suggests an SE for cyclopropene of 54.1 kcal/mol; both values agree quite well with experimentally derived estimates. Since the SE of cyclopropene is essentially twice that of cyclopropane, and both have considerable angle strain, it is more appropriate to think of the SE of the latter as being atypically low rather than the SE of cyclopropene being anomalously large. This disparity may be attributed to the very high C−H bond strengths of cyclopropane.[8]

When the ring contains a C═O or when heterocycles are involved, we prefer the combination with cyclopropane rather than dimerization[14] of the three-member ring heterocycle because the resulting six-member ring reference compound more closely resembles cyclohexane and affords a better opportunity to assess its relative strain energy. This protocol has provided ring strain energies for both hydrocarbons and heterocyclic ring systems in excellent agreement with experiment.[6] However, the accepted SE for cyclopropane is predicated upon the assumption that the SE of cyclohexane is zero; a subject that must now be addressed because some of the resulting six-member reference compounds that we have utilized exhibit strain energies that are far from zero!

The SE that we predict based upon the combination of cyclopropanone with cyclopropane to afford cyclohexanone is 45.1 kcal/mol (Table 2, eq 4), in very good agreement with the SE predicted earlier by Williams et al.[9a] (43 kcal/mol) based upon isodesmic reactions. The dimethyl derivative of cyclopropanone appears to have a slightly higher strain energy (ΔSE = 3.4 kcal/mol). By comparison, the corresponding combination of cyclopropane with methylenecyclopropane to produce methylenecyclohexane suggests a SE = 39.5 kcal/mol (Table 2, eq 3); the accepted SE for methylenecyclopropane is 40.9 kcal/mol.[4a] Thus the impact upon the SE of a carbonyl carbon in a three-member ring is 5.6 kcal/mol greater than that of an trigonal carbon. Intuitively, this relatively high SE can be attributed largely to angle strain since contraction of the H−C−H bond angle in formaldehyde to the internal angle in cyclopropanone (64.4°) results in a 60 kcal/mol increase in energy. The C−H bond dissociation energies (BDEs) of highly strained alkenes play a major role in determining their overall thermodynamic stability and hence their SE. For example, the SE of methylenecyclopropane (39.5 kcal/mol) is reduced to 29.8 kcal/mol (CBS-Q, dimerization) in methylcyclopropane.[6a] Correspondingly, their respective ring C−H BDEs are 97.9 and 109.7 kcal/mol (CBS-APNO, Table 1).

This noted effect of ring C−H BDEs on strain energies prompted a closer look at the C−H BDEs in cyclopropanone. This is of particular interest since hydrogens alpha to a carbonyl group are relatively acidic. We first compared the relative C−H BDEs for acyclic reference compounds isobutylene and acetone and found that the α-carbonyl C−H bond in acetone (96.7 kcal/mol) is 7.5 kcal/mol stronger (CBS-APNO) than the more weakly acidic allylic C−H bonds of isobutylene (89.2 kcal/mol, Table 1). This is an obvious consequence of the fact that the allylic radical derived from C−H bond cleavage in isobutylene is stabilized by delocalization over a three-carbon allylic fragment. Contrariwise, the α-carbonyl radical prefers to have its spin localized on carbon, reflecting the destabilizing consequences of the corresponding oxygen radical ($\Delta E = 23.1$ kcal/mol).[15] Thus, homolytic C−H bond separation in hydrocarbons must be considered differently from proton abstraction adjacent to a carbonyl, where the acidity of these two compounds differs widely ($\Delta pK_a \approx 20-25$). For primarily the same reasons, the BDE of the ring C−H bond in methylenecyclopropane is ∼2 kcal/mol lower than that of cyclopropanone (99.8 kcal/mol, CBS-APNO). The relatively high SE exhibited by cyclopropanone can be attributed largely to its greater angular strain since its C−H bonds still remain much weaker than those of cyclopropane (109.5 kcal/mol, Table 1). Obviously, there are other factors involved, but the increase in the SE of cyclopropanone relative to cyclopropane (ΔSE=17.3 kcal/mol) and its weaker C−H bonds also must be taken into consideration. The SE of 1,1-dimethylcyclopropanone shows only a modest increase (3.4 kcal/mol) relative to that of the parent cyclopropanone. A similar small increase in SE (1.9 kcal/mol)[6a] was noted for 1,1-dimethylcyclopropane based upon the analogous combination scheme in Table 2. However, the effect of *gem*-dimethyl substitution on cyclopropane shows a stabilizing influence of 7−9 kcal/mol[6a] when the relative energies are relevant to *a linear reference molecule*[6b] emphasizing the importance of the choice of the reference molecule. The introduction of a C═C into cyclopropane results in a marked increase in SE for cyclopropene (ΔSE = 26 kcal/mol). However, on the basis of the combination of cyclopropenone with cyclopropane to produce cyclohexenone (not shown), the SE for cyclopropenone is only 8 kcal/mol greater than that of

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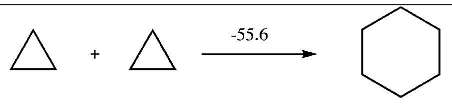
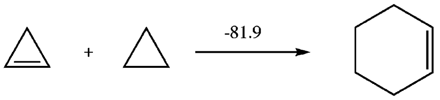
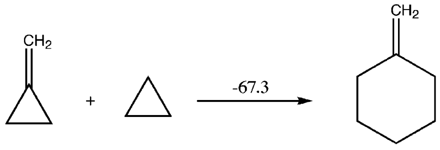
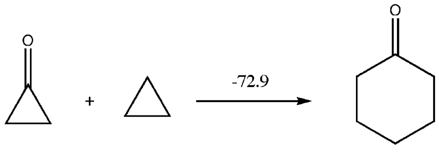
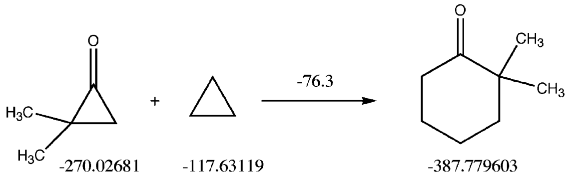
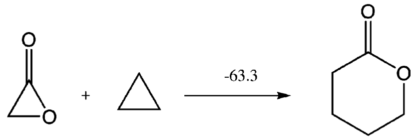
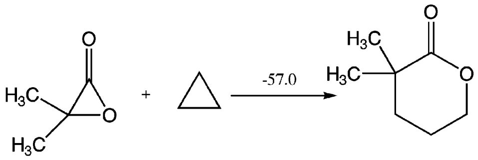
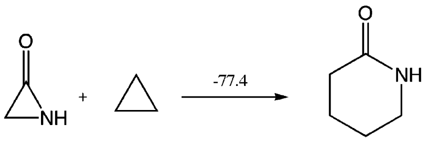
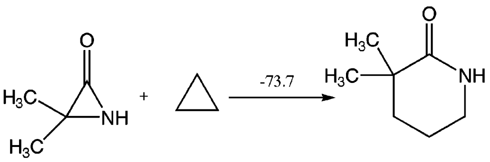
[14] (a) Skancke, A.; Van Vechten, D.; Liebman, J. F.; Skancke, P. N. *J. Mol. Struct.* **1996**, *376*, 461 and references therein. (b) Liebman, J. F.; Skancke, P. N. *Int. J. Quantum Chem.* **1996**, *58*, 707. (c) Zeiger, D. N.; Liebman, J. F. *J. Mol. Struct.* **2000**, *556*, 83. (d) Skancke, A.; Liebman, J. F. *J. Org. Chem.* **1999**, *64*, 6361.

[15] (a) The oxygen radical derived from O−O bond cleavage in isopropenyl hydroperoxide, with the spin on oxygen oriented in the σ plane of the molecule ($\sigma\ ^2A'$) in this case, prefers the electronic spin density on the carbon atom (lower lying $\pi\ ^2A''$ state), resulting in a stabilization energy of 23.1 kcal/mol (G3) due to electron delocalization in the π system. For a discussion, see: Bach, R. D.; Ayala, P. Y.; Schlegel, H. B. *J. Am. Chem. Soc.* **1996**, *118*, 12758.

Table 2. Reaction Energies (kcal/mol, CBS-Q) for the Dimerization/Combination of Substituted Cyclopropanes and Strain Energies Relative to that of Cyclopropane (27.8 kcal/mol)[a]

	equations	reaction energy, kcal/mol	SE, kcal/mol
eq 1	 -117.63119 -117.63119 -235.35097	-55.6	27.8 [25.4]
eq 2	 -116.38185 -117.63119 -234.14352	-81.9	54.1 [51.7]
eq 3	 -155.63466 -117.63119 -273.37314	-67.3	39.5 [37.2]
eq 4	 -191.56578 -117.63119 -309.31312	-72.9	45.1[b] [42.7]
eq 5	 -270.02681 -117.63119 -387.779603	-76.3	48.5 [46.1]
eq 6	 -227.50384 -117.63119 -345.23592	-63.3	35.5[c] [33.1]
eq 7	 -305.97522 -117.63119 -423.69716	-57.0	29.2 [26.8]
eq 8	 -207.61938 -117.63119 -325.37396	-77.4	49.6[d] [47.3]
eq 9	 -286.08637 -117.63119 -403.83505	-73.7	45.9 [43.6]

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[a] Reaction energies and strain energies (kcal/mol, CBS-Q) of substituted cyclopropanes based upon difference between the reaction energy and SE = 27.8 of cyclopropane. SE numbers in brackets are calculated using $-CH_2-$ energy equivalent according to the formula SE = $627.51[E_{3-\text{memeber}} + 3E(-CH_2-) - E_{6-\text{member}}]$, where $E(-CH_2-) = 3(E_{n-\text{hexane}} - E_{n-\text{pentane}})$. [b] The SE is 49.0 kcal/mol after correction for the SE of cyclohexanone. See eqs 16−20. [c] The SE is 47.0 kcal/mol after correction for the SE of δ-valerolactone. [d] The SE is 54.7 kcal/mol after correction for the SE of δ-valerolactam.

cyclopropanone. This should be considered as an approximate SE because cyclohexenone has lower symmetry and only one C=O bond to an sp^2 carbon.

To place the effect of α-carbonyl C−H BDEs in perspective, we also compare directly the C−H BDEs of cyclopropanone with those of cyclobutanone. The α- and β-C−H bonds in cyclobutanone (94.0 and 101.5 kcal/mol, CBS-Q) do not differ markedly from those of the acyclic reference ketone, acetone (97.1 kcal/mol). In similar fashion, the α-C−H bond in methylenecyclobutane (85.0 kcal/mol) is comparable to that in isobutylene (87.1 kcal/mol). In general, the stronger C−H bonds in a three-member ring can be attributed partially to the greater s character in its C−H bonds.[5] Presumably, the increased s character in the cyclopropyl C−H bond leads to an increase in BDE in much the same way as a C−H bond on an $\approx$sp^2 carbon of a C=C. Indeed, the vinyl C−H BDE in ethylene is quite comparable to that in cyclopropane (ΔBDE = 1.6 kcal/mol).

The effect of introducing one or more oxygen atoms into a three-member ring compound also remains controversial. On the basis of this dimerization/combination method, the simplest epoxide, oxirane, is 1.2 kcal/mol less strained than cyclopropane (G2) and the simplest cyclic peroxide, dioxirane, has an SE of only 17 kcal/mol.[6b,c] Thus, the introduction of oxygen atoms into a three-member ring tends to lower its SE in contrast to earlier predictions. Accordingly, combination of the parent α-lactone (oxiranone) with cyclopropane to produce the six-member ring reference lactone, δ-valerolactone, suggests a relative SE (35.5 kcal/mol) that is nearly 10 kcal/mol less than that of cyclopropanone (Table 2). The C−H BDEs of oxiranone (102.9 kcal/mol, CBS-APNO) are only 3.1 kcal/mol greater than those of cyclopropanone. However, as we discuss below, the SE of δ-valerolactone is ca. 8−9 kcal/mol greater than that of cyclohexane (section 3.4), which implies a greater SE for oxiranone (44 kcal/mol) relative to an all-*anti* open chain ester reference molecule. This correction for the SE of the δ-valerolactone reference compound places our estimate of the SE of oxiranone very close to that suggested by Williams (42.7 kcal/mol) based upon an average of two isodesmic reactions.[9a] We see a decrease (ΔSE = 6.3 kcal/mol) in the SE of the dimethyl α-lactone, but we have not attempted to estimate the SE of the dimethyl reference lactone.

Although the simplest aziridine has an SE (27.0 kcal/mol)[6c] that is close to that of ethylene oxide (25.7 kcal/mol), the effect of nitrogen substitution within the cyclopropanone ring has the opposite effect. The predicted SE for the parent α-lactam **7** based upon its combination with cyclopropane is 49.6 kcal/mol (eq 8, Table 2). Despite this surprisingly high SE, its ring C−H BDEs (100.4 kcal/mol) are essentially the same as those in cyclopropanone, but still remain significantly lower than those in cyclopropane (Figure 1). The results for the dimethyl α-lactam are consistent with that noted above for the dimethyl α-lactone with a somewhat smaller decrease in its strain energy (ΔSE = 3.7 kcal/mol).

A method equivalent to combination of the three-member ring compound with cyclopropane for calculating the SE, based upon computed total energies that include zero-point energy corrections, is to simply include one-half the total energy of cyclohexane, where SE = ($E_{\text{cyclopropane}}$ + 1/2 $E_{\text{cyclohexane}}$) − $E_{\text{cyclohexane}}$ gives an SE = 27.2 kcal/mol at the G2 level of theory and 27.8 kcal/mol at the CBS-Q level, in excellent agreement with experimentally derived SE (27.5 kcal/mol).[4a] Of course, this three-carbon fragment contains the one-half of the inherent *nonzero* ring strain of cyclohexane, and as we reiterate, the accepted SE of cyclopropane is predicated upon the assumption that the SE of cyclohexane is zero. This problem is exacerbated at the CBS-Q level since the SE per CH$_2$ group is 0.78 kcal/mol (see below).

Table 3. Total Energies of Alkanes and Derived Energies of $-CH_2-$ Fragment Calculated at the CBS-Q, CBS-APNO, and G3 Levels of Theory

compound	*E* (au)	E_{-CH_2-} (au)
	CBS-Q (0 K)	
n-pentane	−197.30750	
n-hexane	−236.53393	39.22643
n-heptane	−275.76005	39.22612
n-octane	−314.98602	39.22597
n-decane	−393.44015	39.22707
cyclohexane	−235.35097	39.22516
	average E_{-CH_2-} (au)	**39.22640**
	SE per $-CH_2-$ group of cyclohexane	**0.78 kcal/mol**
	CBS-APNO (0 K)	
n-pentane	−197.60007	
n-hexane	−236.88430	39.28424
cyclohexane	−235.70196	39.28366
	average E_{-CH_2-} (au)	**39.28424**
	SE per $-CH_2-$ group of cyclohexane	**0.36 kcal/mol**
	G3 (0 K)	
n-pentane	−197.53577	
n-hexane	−236.80679	39.27102
n-heptane	−276.07784	39.27106
n-octane	−315.34891	39.27107
cyclohexane	−235.62288	39.27048
	average E_{-CH_2-} (au)	**39.27105**
	SE per $-CH_2-$ group of cyclohexane	**0.36 kcal/mol**

Alternatively, perhaps a more accurate estimate can come from including the energy of three CH$_2$ equivalents derived from an all-*anti* strain-free hydrocarbon taken from the difference in the total energies of *n*-hexane minus *n*-pentane (Table 3). This suggests an SE for each of the cyclic compounds in Table 2 that is reduced by about 2.4 kcal/mol. However, when we include the strain energy of cyclohexane (2.2 kcal/mol), these calculated SEs remain approximately the same.

3.3. The Strain Energy of Cyclohexane Based upon CH$_2$ Energy Equivalents. As discussed in the Introduction, the oft-quoted SE for cyclopropane of 27.5 kcal/mol arises from the observation that the experimental ΔH_f = −4.926 kcal/mol for the normal methylene fragment for a straight-chain hydrocarbon is essentially identical to that of cyclohexane (−4.92 kcal/mol per CH$_2$ group).[4a] Because of this close agreement in the heat contents, cyclohexane has generally been taken as strain free. However, a comparison of the experimental $\Delta H°_{f(liq)}$ = −37.39 kcal/mol of cyclohexane with the difference in $\Delta H°_{f(liq)}$ for *n*-hexane (−47.48 kcal/mol) versus *n*-pentane (−41.47 kcal/mol) suggests a $\Delta\Delta H°_{f(liq)}$ of 0.22 kcal/mol (per CH$_2$) or a SE for cyclohexane of 1.3 kcal/mol. We recently carried out his same exercise at a high level of ab initio theory (G2) comparing ΔH_{298} and suggested a $\Delta\Delta H_{298}$ = 0.26 kcal/mol (per CH$_2$) or an of SE of 1.6 kcal/mol for cyclohexane.[6a] The suggestion of a nonzero SE in cyclohexane is not a new idea since Schleyer, in an insightful report several decades ago,[3] suggested a modest strain for cyclohexane (1.35 kcal/mol) and also provided an explanation for why the presumably strain-free adamantane has an SE of 6.5 kcal/mol. Wiberg[4a] has also proffered that while the normal methylene increment for a straight-chain hydrocarbon is very close to that of cyclohexane this is a consequence of the fact that only a minor percentage of a linear hydrocarbon mixture actually resides in their ground-state *anti*-conformations. The gauche conformations predominate since there is only one *anti*-conformation, while there are many possible gauche conformations in dynamic equilibrium. Since the above dimerization/combination schemes use a six-member ring reference compound, we examine more closely the SE of cyclohexane and its archetypal partner, cyclopropane, to reconcile this recurring controversy.

Cyclohexane has six gauche C−C−C−C torsional angles. While all-*anti* *n*-hexane is obviously free of ring strain, its optimized conformation with two gauche angles ($\theta = 64.5°$) is 1.4 kcal/mol (CBS-APNO) higher in energy. The gauche minimum for *n*-butane is 0.69 kcal/mol higher in energy than the all-*anti* ground state, and the eclipsed TS ($\theta = 120.0°$) for torsion about the central C−C bond is 3.37 kcal/mol higher in energy (CBS-APNO). Thus, the experimental observation that the normal methylene energy increment for straight-chain hydrocarbons, −4.93 kcal/mol, is essentially identical to that of cyclohexane is coincidental. Since these linear hydrocarbon reference compounds quite logically have many different, higher energy, gauche conformations than the all-*anti* ground state, the CH_2 fragment energy should be somewhat more negative than −4.93 kcal/mol,[4a] and this concurs with the earlier suggestions that, in fact, cyclohexane should have a nonzero strain energy.[3,4]

The use of the all-*anti* hydrocarbon as a reference compound simply derives from the fact that it is a practical “hypothetical” point of reference. It must be emphasized that the thermodynamics have not changed in this problem and it is the reference compound that remains the point of contention. Since the SE of cyclohexane is germane to the SE of cyclopropane, a fundamental “yardstick” for the assessment of ring strain, we revisit this point at several levels of theory. Theoretical calculations have reached a point where we can repeat the above thermodynamic measurements computationally at a high level of ab initio theory and have confidence in the resulting data. Initially, we used the energy difference between *n*-hexane and *n*-pentane to calculate the incremental CH_2 energy at the CBS-Q, G3, and, where possible, the CBS-APNO methods. We also included several higher normal alkanes to ensure that the CH_2 energy increment had reached a maximum. We find average CH_2 energy values of 39.22640, 39.28424, and 39.27105 au at the CBS-Q, CBS-APNO, and G3 levels of theory, respectively. The corresponding energy equivalents derived per CH_2 group in cyclohexane, derived by simply dividing the total energy of cyclohexane by six, by these three methods are 39.22516, 39.28366, and 39.27048 au (Table 3). From these data, we calculate an SE for cyclohexane per CH_2 group of 0.778, 0.364, and 0.358 au. This suggests an SE for cyclohexane by the three methods of 4.67, 2.18, and 2.15 kcal/mol. The results from the CBS-Q method are somewhat disappointing in this exercise, where the problem appears to be related to the single calculation on the total energy of cyclohexane. The geometry optimization for both the CBS-Q and G3 methods is at the MP2/6-31(d) level, while that for the CBS-APNO is at QCISD/6-311G(d,p).

Another measure of the accuracy of the theoretical method to estimate this CH_2 energy equivalent is to calculate the single triplet energy gap for methylene. The experimental energy gap is 9.0 kcal/mol,[16] and the theoretical values at the CBS-Q, G3, and CBS-APNO levels are 8.11, 9.49, and 8.97 kcal/mol. At the more reliable CBS-APNO level, this exercise that mimics the experimental determination of the $-CH_2-$ increment as closely as possible suggests an SE of 2.2 kcal/mol for cyclohexane. An earlier estimate for the SE of cyclohexane at the G2 level was 2.4 kcal/mol.[6c]

The strain energy of cyclohexane, relative to the strain-free reference compound, all-*anti* *n*-hexane, can also be calculated using the energy terms balancing the difference in the number of atoms and bonds in the cyclic versus the acyclic molecules. This protocol, reported recently by Dudev and Lim,[1d,17] provides a very practical method to estimate the strain energy where the total energy is adjusted for the removal of two hydrogen atoms and formation of the C−C bond attending cyclization. Employing this cyclization method,[1d] a strain energy for cyclohexane of 2.5 kcal/mol (MP2/6-31+G*)[1d] and 2.4 kcal/mol (G2)[6c] relative to the strain-free reference compound, all-*anti* *n*-hexane, has been reported.

3.4. Strain Energies of Six-Member Ring Reference Compounds Derived from Homodesmotic Reactions. Early attempts to estimate strain energies of small cyclic compounds used isodesmic reactions where the formal bonds were separated into the simplest molecules with the same bond type. Later, homodesmotic reactions[18] were introduced that attempted too more closely match the C−C bond types and the various types of C−H bonds on each side of the equation. An improved method for estimating SEs was subsequently introduced by Bachrach[19] that utilized group equivalent reactions that are homodesmotic and also conserve the chemical group equivalency. The earliest homodesmotic equation to estimate the SE of cyclopropane (cyclopropane + 3 ethane = 3 propane)[18] when estimated at a relatively high ab initio level(G2) suggests an SE of 27.3 kcal/mol.[6] This value is in excellent agreement with experiment (27.5 kcal/mol), despite the fact the bond dissociation energies (BDE) for the secondary C−H bonds in propane are poorly matched with the primary C−H bonds in ethane. The CBS-APNO, G3, and CBS-Q methods provide SEs of 27.50, 27.54, and 27.45 kcal/mol. This remarkable agreement (Table 4) is not maintained at the B3LYP/6-31G(d) level (SE = 29.1 kcal/mol) or when the flexibility of the basis set is increased (B3LYP/6-311+G(3df,2p), SE = 25.8 kcal/mol). However, at the APNO level when cyclopropane is balanced with propane affording *n*-hexane, the calculated SE is 28.3 kcal/mol, in excellent agreement with our most recent estimate.

In a recent comprehensive study of bi- and tricyclic ring systems, the homodesmotic equation was typically balanced with ethane on one side of the equation (B3LYP/6-31G*).[1a] As the ring size increased, the *n*-alkane was lengthened accordingly but ethane was always maintained in the basic equation. The

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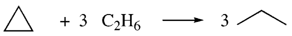
(16) Leopold, D. G.; Murray, K. K.; Miller, A. E. S.; Lineberger, W. C. *J. Chem. Phys.* **1985**, *83*, 4849.

(17) For a description of the details for cyclization of *n*-hexane to cyclohexane, see ref 1d. For a series of parameters used for cyclization of a variety of substrates at the G2 level, see ref 6c.

(18) For earlier examples of the use of homodesmotic reactions, see: (a) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *Tetrahedron* **1976**, *32*, 317. (b) George, P.; Trachtman, M.; Brett, A. M.; Bock, C. W. *J. Chem. Soc., Perkins Trans. 2* **1977**, 1036.

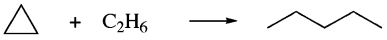
(19) Bachrach, S. M. *J. Chem. Educ.* **1990**, *67*, 907.

Table 4. Reaction Energy and Enthalpy for the Prediction of the SE of Cyclopropane Calculated at Different Levels of Theory



method	ΔE (kcal/mol)	ΔH (kcal/mol)
G3	−27.55	−28.23
CBS-Q	−27.45	−28.16
CBS-APNO	−27.50	−28.22
B3LYP/6-31G(d)	−29.05	−26.67
B3LYP/6-311+G(3df,2p)	−25.80	−23.56

use of ethane was largely based upon necessity when the size of the systems treated in that study was taken into consideration. Nonetheless, this study provided a great many useful estimates of the SE of very complex molecules.

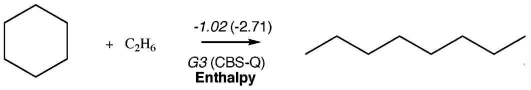


(eq 10)

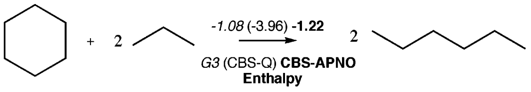
The homodesmotic scheme in eq 10 does ensure that the number of atom and bond types are conserved in the two terms on the left-hand side. However, the BDEs in ethane do not always match with those in the long-chain *n*-alkane reference molecule. In this basic equation (eq 10), the acyclic reference compound has three secondary carbons and two primary carbons. Sometimes these equations do give you the “correct” answer because of cancellation of errors. For example, the DFT (B3LYP/6-31G(d)) performance for the C−C bond in CH_3−CH_3 (89.17 kcal/mol) fortuitously provides a value close to the experimental BDE (89.87 kcal/mol). However, B3LYP/6-311++G(d,p) and B3LYP/6-311++G(3df,2p) both show an underestimation of about 5 kcal/mol.[20] The series of C−C bond energies given in Table 5 show good agreement with the experimental BDE for ethane, but the experimental BDEs for the C−C bond in propane appear to be low by several kcal/mol. In general, the G3 method provides C−C BDEs that are about 1.5 kcal/mol lower than those at CBS-APNO and CBS-Q, with the latter two methods, however, being in good agreement with each other. The combined data do demonstrate that the C−C BDEs do level off at a fairly small number of carbon atoms in the *n*-alkane chain.

There are somewhat more experimental data available for C−H bond energies, although these values are often not in very good agreement with each other because they are derived from a series of experimental multi-step bond breaking and bond making reactions that can result in considerable error. There is remarkably good agreement between theory and experiment for the series of C−H BDEs in Table 6. Unfortunately, it is difficult to go much beyond pentane at the APNO level because calculations on open-shell radicals require considerable computational resources.

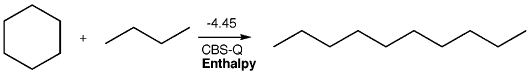
With these specific BDEs in hand, it is possible to assess the SE of cyclohexane from the vantage point of well-balanced homodesmotic reactions. The approach of Goddard[1a] (eq 10) using ethane as a reference molecule provides an SE for cyclohexane of 1.0 kcal/mol (eq 11). At the G3 level, one sees a gradual increase in this SE as the length of the alkane on the left side of the equation increases (eqs 11−14), but the SE only reaches about one-half of the 2.2 kcal/mol predicted by the above assignment based upon the more reliable CH_2 energy equivalents method (section 3.3). The SE for cyclohexane predicted by the CBS-Q method does approach that given above based upon CH_2 energy equivalents (4.7 kcal/mol), but again better agreement is reached as the size of the alkane reference compound increases.



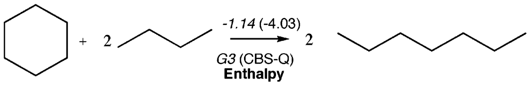
(eq 11)



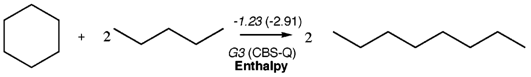
(eq 12)



(eq 13)

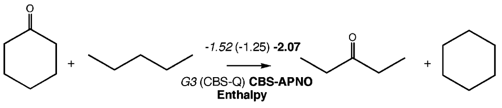


(eq 14)

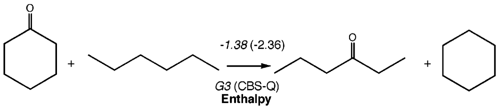


(eq 15)

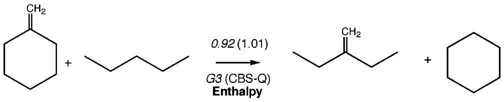
We also use a comparable series of balanced homodesmotic reactions[18] to assess the SE of several six-member ring reference compounds *relative to that of cyclohexane* at both the G3 and CBS-Q levels (eqs 16−20). The carbonyl group in cyclohexanone is balanced with 3-pentanone in eq 16 rather than with acetone (isodesmic approach) since the methyl groups in acetone are alpha to the C═O and this has two more α-keto hydrogens than cyclohexanone.



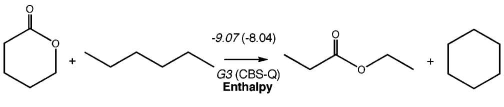
(eq 16)



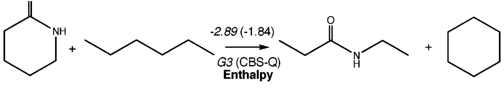
(eq 17)



(eq 18)



(eq 19)



(eq 20)

For similar reasons, we prefer to use *n*-pentane or *n*-hexane to balance the equation rather than propane. The effect of the C═O on a CH_2 energy equivalent β to a C═O is less than that of an α-CH_2 group (ΔE = 0.65 kcal/mol, see Supporting Information). The SE of cyclohexanone, relative to reference compound 3-hexanone, is slightly increased (eq 17). On the basis of the data at the CBS-APNO level, we suggest that cyclohex-

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(20) Feng, Y.; Liu, L.; Wang, J. T.; Huang, H.; Guo, Q. X. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 2005.

Table 5. C−C BDEs (kcal/mol) of *n*-Alkanes

compound	G3	CBS-APNO	CBS-Q	expt
$CH_3{-}CH_3$	88.36	**90.67**	90.05	89.7 ± 0.5[a] 90.4[a]
$CH_3CH_2{-}CH_3$	87.99	**89.73**	89.45	85.8,[b] 88.2[c]
$CH_3CH_2CH_2{-}CH_3$	88.44	**90.15**	90.27	86.2[d]
$CH_3CH_2{-}CH_2CH_3$	87.75	**88.88**	89.34	
$CH_3CH_2CH_2CH_2{-}CH_3$	88.40	**90.09**	90.02	
$CH_3CH_2CH_2{-}CH_2CH_3$	88.18	**89.29**	90.98	
$CH_3CH_2CH_2CH_2CH_2{-}CH_3$	88.41		90.62	
$CH_3CH_2CH_2CH_2{-}CH_2CH_3$	88.16	**89.25**	90.14	
$CH_3CH_2CH_2{-}CH_2CH_2CH_3$	88.63	**89.72**	91.70	
$CH_3CH_2CH_2CH_2CH_2{-}CH_2CH_3$	88.20		90.55	
$CH_3CH_2CH_2CH_2{-}CH_2CH_2CH_3$	88.64		91.00	
$CH_3CH_2CH_2CH_2CH_2{-}CH_2CH_2CH_3$	88.68		91.31	
$CH_3CH_2CH_2CH_2{-}CH_2CH_2CH_2CH_3$	88.64		90.19	

[a] *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed.; CRC Press LLC: Boca Raton, Florida, 2002. [b] The BDEs are taken from Baghal-Vayjooee, M. H.; Benson, S. W. *J. Am. Chem. Soc.* **1979**, *101*, 2838 and Vreven, T.; Morokuma, K. *J. Chem. Phys.* **1999**, *111*, 8799. [c] On the basis of experimental heats of formation of methyl radical, ethyl radical, and propane (NIST *Standard Reference Database*; see ref 2b). [d] The BDEs are taken from Johnson, W. T. G.; Borden, W. T. *J. Am. Chem. Soc.* **1997**, *119*, 55930.

Table 6. Experimental[a] and Theoretical C−H BDEs (kcal/mol) of Alkanes

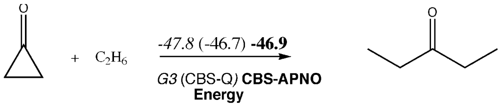
compound	G3	CBS-APNO	CBS-Q	expt
$H{-}CH_3$	104.2	**105.4**	105.1	104.9 ± 0.1
$H{-}CH_2CH_3$	101.2	**101.8**	101.7	
$H{-}CH_2CH_2CH_3$	101.5	**102.1**	102.0	101.2 ± 0.5, 101.0[b]
$CH_3\,(CH{-}H)CH_3$	98.9	**99.1**	99.2	97.8 ± 0.5, 99.1,[b] 98.6,[c] 99.4[d]
$H{-}CH_2CH_2CH_2CH_3$	101.5	**102.1**	101.3	101.7 ± 0.5
$CH_3(CH{-}H)CH_2CH_3$	99.2	**99.4**	99.5	98.3 ± 0.5
$(CH_3)_3C{-}H$	97.4	**97.4**	97.8	96.6 ± 0.3
$H{-}CH_2CH_2CH_2CH_2CH_3$	101.5		102.1	
$CH_3\,(CH{-}H)CH_2CH_2CH_3$			99.4	
$CH_3CH_2(CH{-}H)CH_2CH_3$		**99.7**		

[a] *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed.; CRC Press LLC: Boca Raton, Florida, 2002. [b] On the basis of experimental heats of formation of methyl radical, ethyl radical, and propane (NIST *Standard Reference Database*; see ref 2b). [c] The values are taken from Seakins, P. W.; Pilling, M. J.; Niiranen, J. T.; Gutman, D.; Krasnoperov, L. N. *J. Phys. Chem.* **1992**, *96*, 9847. [d] The BDEs are taken from Johnson, W. T. G.; Borden, W. T. *J. Am. Chem. Soc.* **1997**, *19*, 55930.

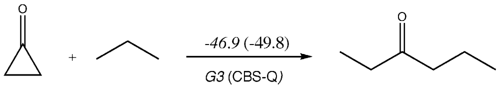
anone has an SE of 2.1 kcal/mol relative to cyclohexane and 4.3 kcal/mol when corrected for the SE of cyclohexane based upon an all-*anti* alkane reference molecule. Using isodesmic equations (acetone and propane), the SE of cyclohexanone relative to cyclohexane at the G3 and CBS-Q levels is reduced to 0.97 and 0.94 kcal/mol, reinforcing the idea of using well-balanced homodesmotic equations. Bachrach[19] first emphasized the importance of using well-balanced homodesmotic equations when he introduced the concept of group equivalent reactions.

Methylenecyclohexane has an SE of ca. 1.2 kcal/mol since it is found to be ca. 1 kcal/mol *less strained than cyclohexane* (eq 18). However, as noted above, the SE of δ-valerolactone is estimated to be 8−9 kcal/mol greater than that of cyclohexane (SE = 11.3 kcal/mol based upon G3 values), and this clearly cannot be considered as a strain-free reference compound. We also examined several conformations of this δ-valerolactone and are reasonably sure that we have the global minimum. The same holds true for the acyclic reference ester that prefers to be in what is essentially an all-*anti*-conformation without geometry constraints. The six-member ring lactam, δ-valerolactam, is also moderately strained with an estimated SE of 5.1 kcal/mol, including the correction for the SE of cyclohexane. In this case, the global minimum of the acyclic amide did not exist in an all-*anti*-conformation. However, when the reference amide was constrained to be all-*anti*, it was only 0.2 kcal/mol higher in energy than the minimum.

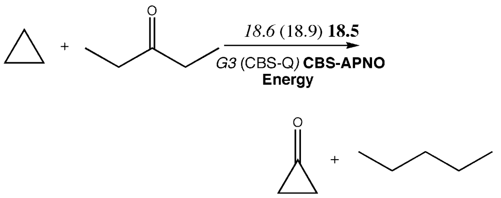
We also use several selected homodesmotic equations that are not related to cyclohexane to check upon the internal consistency of these data. For example, eq 21 suggests an SE for cyclopropanone of 46.9 kcal/mol (CBS-APNO), and eq 22 suggests the comparable SE of 49.8 kcal/mol (CBS-Q); the latter value is in very good agreement with the corrected SE of 49 kcal/mol.



(eq 21)

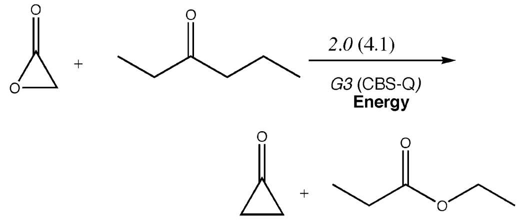


(eq 22)

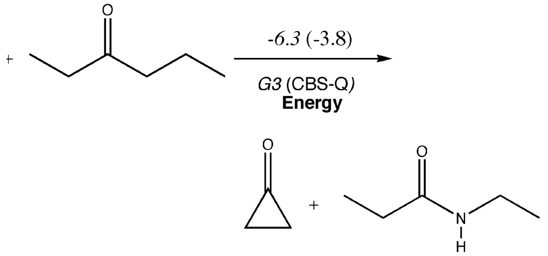


(eq 23)

The combined data thus far suggest that the SE of cyclopropanone is 20.5 kcal/mol greater than that of cyclopropane. Homodesmotic eq 23 predicts that cyclopropanone has an SE that is 18.6 kcal/mol higher than cyclopropane with the G3 method. The change in enthalpy for this reaction at the APNO level suggests a ΔSE = 19.4 kcal/mol. When homodesmotic eq 23 is examined based upon experimental heats of formation, the $\Delta H^{\circ}_{f(298)} = 15.5$ kcal/mol.[21] The combination protocol (Table 2) data also suggest that cyclopropanone has an SE that is just 2 kcal/mol higher than that of the parent α-lactone **6**, and this prediction is corroborated exactly by eq 24 (G3). An independent check upon the SE of α-lactam **7** derives from eq 25 (G3), suggesting a ΔSE = 6.3 kcal/mol, in excellent agreement with the above method based upon the CH_2 combination protocol after correction for the SE of cyclohexane (ΔSE = 6.0 kcal/mol).



(eq 24)



(eq 25)

These data do present a dilemma since one of the pragmatic features of the dimerization/combination protocol is the convenience of the six-member "strain-free" reference compound. We suggest the continued use of this simplified method of relating strain energies to what has become historically the quintessential strain-free cyclic hydrocarbon, cyclohexane, because it is of considerable use to the practicing synthetic chemist to retain a conversational knowledge of the SE of all of the ring systems encountered in the total synthesis of a complex molecule. As a point of calibration, the currently accepted SEs for the simplest series of unsubstituted cyclic hydrocarbons, such as cyclohexane (SE = 0.0 kcal/mol), have *relative* strain energies of cyclopentane (6.2 kcal/mol), cyclobutane (26.5 kcal/mol), and cyclopropane (27.5 kcal/mol).[4a] This is clearly more useful information than the SE relative to some hypothetical reference compound that is never actually encountered. However, since there is no substitute for the correct answer, and because we are now capable of refining these SE values, we also provide the SE corrected for the nonzero strain energy of the reference compounds.

3.5. The Effect of Heteroatom Substitution on Ring Strain. We have discussed briefly the effect upon ring strain energy of the substitution of functional groups into a three-member ring. The influence of an oxygen atom or a nitrogen atom has also been shown to be minimal, with the resulting SE being comparable to that of cyclopropane. However, we see an entirely different effect for the second row elements, Si, P, and S. On the basis of the CH_2 energy equivalent method, the SE of silacyclopropane (Figure 2) shows a decided increase (SE = 33.3 kcal/mol) relative to the hallmark carbocycle, cyclopropane, while phosphorus and especially sulfur evidence a marked decrease in SE. Combination of the three-member ring heterocycle with cyclopropane to produce the corresponding six-member ring reference compound shows a slightly higher SE than that derived from the inclusion of three CH_2 energy equivalents. As noted above, this reflects the correction for the inherent built-in strain of cyclohexane in the combination protocol. The noted trend in both the increase and decrease in SE relative to cyclopropane is clearly not a function of the C−H BDE in this series of heterocyclic three-member ring compounds because the C−H BDEs remain within a 102−106 kcal/mol range. The greater length of the C−X bond in these second row compounds increases the C−X−C angle and the bending frequency that has a major impact upon the SE.

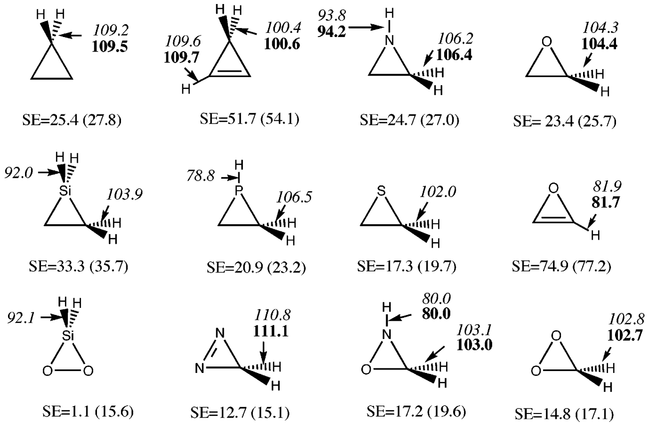


Figure 2. BDE (kcal/mol) calculated at G3 (italic) and CBS-APNO (bold) levels. SE (kcal/mol) is calculated using 3 $-CH_2-$ equivalents (*n*-hexane − *n*-pentane) at the CBS-Q level. The SEs, in parentheses, are based upon dimerization with cyclopropane.

The effect of the introduction of two heteroatoms into a three-member ring has been a subject of controversy for a number of years.[6b,c] The ring strain of dioxirane was initially reported to be quite high when the SE was derived from homodesmotic reactions. This, however, has been shown[6b,c] to be an artifact of the imbalance of homodesmotic reactions involving the *gem*-diol functionality, $H_2C(OH)_2$. Although, as demonstrated above, while the SEs derived from homodesmotic reactions are remarkably good for hydrocarbons, they prove to be equally poor for ethers and especially peroxides.[6]

It was the realization that the initial high assessment of the SE of the parent dioxirane (DO) and related dioxiranes could not account for the relatively poor reactivity of dimethyldioxirane (DMDO) toward alkenes[22] that brought us into this controversial area of ring strain. We assigned initially an SE for DO of only 17 kcal/mol and an even lower SE for DMDO. However, it must be strenuously emphasized that the concept of greater chemical reactivity associated with highly strained hydrocarbons does not necessarily translate to the reactivity of dioxiranes. Quite the opposite is true. Although the SE of

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(21) With a $\Delta H^{\circ}_{f(298)}$ derived from the experimental heat of formation of propene (4.879 kcal/mol)[3] and a calculated $\Delta H^{\circ}_{f(298)}$ between propene and cyclopropane (7.718 kcal/mol), the $\Delta H^{\circ}_{f(298)}$ for cyclopropane at the APNO level is 12.6 kcal/mol compared to an earlier estimate of 12.74 kcal/mol.[9a] The same procedure with propenal ($\Delta H^{\circ}_{f(298)} = -18.403$ kcal/mol) and a calculated enthalpy difference (19.735 kcal/mol) with cyclopropanone gave a $\Delta H^{\circ}_{f(298)} = 1.33$ kcal/mol. The experimental $\Delta H^{\circ}_{f(298)}$ for 3-pentanone and *n*-pentane are −61.8 and −35.08 kcal/mol, respectively. The reaction energy is very close to that reported in ref 9a (15.5 kcal/mol) based upon a similar exercise.

(22) Bach, R. D.; Dmitrenko, O.; Adam, W.; Schambony, S. *J. Am. Chem. Soc.* **2003**, *125*, 924.

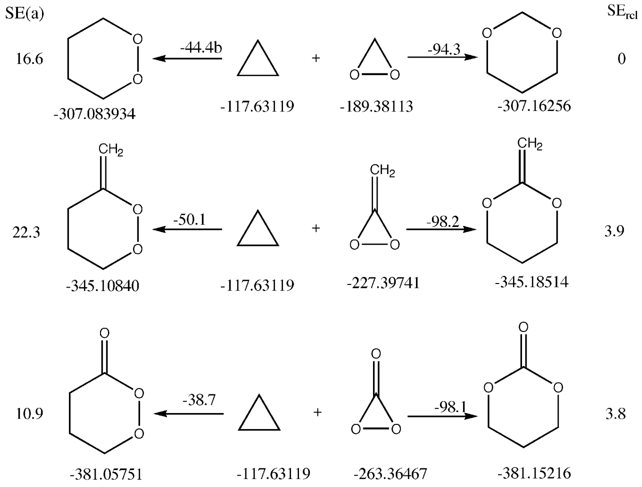


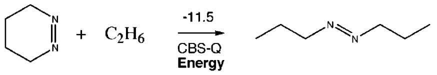
Figure 3. CBS-Q dimerization energies, SE (kcal/mol), and relative SE_{rel} (kcal/mol, with respect to DO) based upon dimerization to 1,2-dioxa (left) and 1,3-dioxa (right) six-member ring compounds. (a) On the basis of that estimated at CBS-Q strain energy of cyclopropane SE = 27.8 kcal/mol; the SE of dioxirane is 18 kcal/mol (see refs 6b and 6c); (b) G2(MP2).

DMDO is only 11 kcal/mol,[6b,c] based upon the traditional concepts used to assess strain energy, this cyclic peroxide is still a very high energy reagent as a consequence of it high energy peroxide bond.

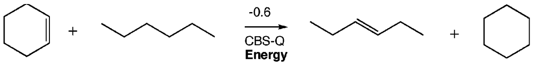
By convention, the acyclic peroxo reference compounds also have high energy O−O bonds. This is demonstrated by simply considering the relative energies of 1,3-, 1,4-, and 1,2-dioxanes (0.0, 5.7, and 49.3 kcal/mol). For example, isomerization of 1,2-dioxacyclohexane, possessing a weak peroxide bond (O−O BDE = ca. 40 kcal/mol),[15] to its 1,3-isomer is attended by the liberation of 49.3 kcal/mol (CBS-Q), reflecting the two much stronger C−O bonds in the latter isomer. This striking energy difference is also evident from using the combination protocol with dioxirane, suggesting an SE of 16.8 kcal/mol (Figure 3) and a decrease in total energy of 94.3 kcal/mol upon formation of the 1,3-dioxane. When an *exo*-methylene group is introduced into the dioxirane ring, the SE is only slightly higher at 22.3 kcal/mol. However, of particular relevance to the current topic, the SE of the three-member ring cyclic peroxo carbonate has an estimated SE of only 10.9 kcal/mol, clearly deviating from the trend noted upon substitution of a carbonyl group into a three-member ring producing cyclopropanone. These SE estimates are, of course, based upon the premise of a zero SE for the six-member ring reference compounds, and this appears to be problematic for two of these reference molecules.

The trend for reduced strain energy upon substitution of two heteroatoms into a three-member ring continues for oxiziridine with an estimated SE of only 17.2 kcal/mol (Figure 2). In an earlier study, we suggested that the inclusion of this N−O bond in a three-member ring had an SE of 18.8 kcal/mol at the G2MP2 level.[6c] A particularly striking example of the relatively low SE for diheteroatom substitution is exemplified by diazacyclopropene. For example, 3-H-diazirine, with a N═N double bond (1.25 Å) in a three-member ring, has a predicted SE of only 12.7 kcal/mol based upon its combination with cyclopropane. The C−H BDE in diazirine is also the strongest of all the three-member ring compounds, including cyclopropane at 111.1 kcal/mol (Figure 2). The SE is estimated to be 15.1 kcal/mol based upon the addition of 3 CH_2 energy equivalents. Wiberg[23] recently suggested an SE of 19.8 kcal/mol (MP2) for diazacyclopropene based upon this method. It was also noted that 1,2-diazacyclopentene was 7.1 kcal/mol less strained than the six-member ring reference compound that we have used. This is, therefore, clearly another example where the combination protocol is limited when the SE of the six-member ring reference compound is decidedly nonzero.

We also estimate an SE for diazacyclohexene by using homodesmotic eq 26, where the SE relative to the *trans* isomer is 11.5 kcal/mol. Since the energy difference between *cis*- and *trans*-diazaoctene isomers is 5.4 kcal/mol, the SE of diazacyclohexene is only 6.1 kcal/mol relative to the reference isomer that contains the *cis* arrangement of the N═N bond as in diazacyclohexene. This same problem arises when trying to assign an SE to cyclohexene (eq 27). The energy difference between the *E*- and *Z*-3-hexenes is 2.05 kcal/mol (CBS-Q).



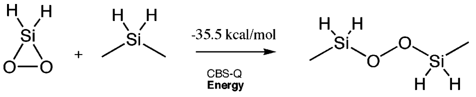
(eq 26)



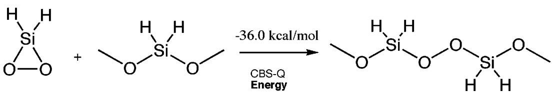
(eq 27)

Therefore, one must either choose a calculated SE of 0.60 kcal/mol with respect to the lower energy *E*-isomer or decide that the SE of cyclohexene is actually 1.45 kcal/mol *less strained* than cyclohexane. Since the *Z*-isomer of the reference compound more closely resembles cyclohexene, we prefer to think that the unsaturation in the molecule lowers its SE relative to cyclohexane.

Finally, we address two examples that clearly do not respond favorably to this method for two very different reasons. The SE of oxirene, where a double bond is introduced into the oxirane ring system, is estimated to be exceptionally high (SE = 74.9 kcal/mol, Figure 2). However, this value is questionable since the radical derived from C−H bond dissociation has an atypically long O−C bond of 1.72 Å. Consequently, the assigned SE should be taken with caution. Another very obvious example is that of siladioxirane, where the SE, based upon the three CH_2 protocol, is only 1.1 kcal/mol. This is an obvious example because the trend noted for silacyclopropane evidences an SE that is markedly increased. However, the sharp decrease in the SE of dioxirane itself (SE = 16−17 kcal/mol) gives cause to ponder. This question, however, is quickly resolved by examination of homodesmotic eqs 28 and 29 that suggest an SE for siladioxirane of 35.5 and 36.0 kcal/mol. This particular example demonstrates the need to have balanced equations in our combination method because a close examination shows that the six-member reference compound derived from the combination of siladioxirane with cyclopropane (eq 30) has only one Si−O bond and the strength of such a bond is both dominant and critical to the success of this method.

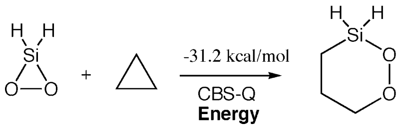


(eq 28)



(eq 29)

According to this protocol, the SE of siladioxirane is only 3.4 kcal/mol, assuming that six-member reference compound is strain free and the SE of cyclopropane is 27.7 kcal/mol at the CBS-Q level.



(eq 30)

3.6. Comparative SE Based upon the Energetics of the Insertion/Extrusion of $-CH_2-$ Energy Equivalents into Cyclic Molecules. We have recently demonstrated a method for determining the strain energies of a variety of cyclic molecules, including the dioxiranes, by incremental ring expansion/contraction with methylene ($-CH_2-$) and oxygen atom ($-O-$) fragments.[6c] The formal insertion of a $-CH_2-$ fragment into a molecule and deriving the SE from differences in the total energies has proven to be a reasonably accurate method when the energy equivalents are obtained at the G2, G3, or CBS-Q levels. A series of reactions that provide α- and β-CH$_2$ energy equivalents (CBS-Q) for vinyl, carbonyl, ester, and amide functionalities are given in Supporting Information. For example, since the SE of methylenecyclobutane is known (26.9 kcal/mol),[4] the SE of methylenecyclopropane can be estimated by extrusion of an α-CH$_2$ fragment (39.22415 au) from the four-member ring of methylenecyclobutane. The differences in total energy suggest that methylenecyclopropane plus a α-CH$_2$ fragment is 12.98 kcal/mol higher in energy than methylenecyclobutane, suggesting an SE $=$ 39.9 kcal/mol for methylenecyclopropane, a value essentially equal to the SE predicted above by its combination with cyclopropane (eq 3, Table 2). Using the reverse procedure, insertion of a β-CH$_2$ fragment (39.22617 au) into methylenecyclobutane gives a total energy difference with methylenecyclopentane of 21.48 kcal/mol. Thus, the SE of methylenecyclopentane is predicted to be just 5.4 kcal/mol; its experimental SE $=$ 6.1 kcal/mol.[4] Although the experimental estimate[4b] for the SE of methylenecyclohexane, based upon heats of formation, is negative (-1.1 kcal/mol),[4a] we suggest an SE $=$ 1.7 kcal/mol based upon extrusion of a β-CH$_2-$ producing methylenecyclopentane. Relative to cyclohexane, we have suggested an SE of 1.2 kcal/mol for methylenecyclohexane (eq 18). Successive extrusion of an α-CH$_2-$ and two β-CH$_2$ fragments from methylenecyclohexane (SE $=$ 1.2 kcal/mol) suggests an SE for methylenecyclopropane of 40.1 kcal/mol. The SE for methylenecyclopropane is also in good agreement with the SE derived from the above dimerization protocol (eq 3), despite the fact that it is based upon three successive $-CH_2-$ extrusion reactions.

This method also gives excellent SEs for simple cyclic alkenes. On the basis of the SE of cyclohexene (0.6 kcal/mol, eq 27), the SEs of cyclopentene (4.7 kcal/mol), cyclobutene (29.5 kcal/mol), and cyclopropene (54.1 kcal/mol) are all within 1 kcal/mol of the accepted strain energy for these compounds.[4] The estimated SE for cyclopropene is identical to that predicted by the combination protocol (eq 2).

As noted above, the SE of the six-member ring reference compound can also be estimated by the cyclization protocol described earlier by Dudev and Lim.[1d] This method provides an internal check upon the SE estimated by homodesmotic equations and by this insertion protocol. At the CBS-Q level, we estimate an SE for cyclohexane of 2.2 kcal/mol upon cyclization of reference compound all-*anti n*-hexane, in excellent agreement with the SE arrived at by several other methods.[6] Likewise, the SE predicted for cyclohexanone (Figure 4) is a little higher (ΔSE $=$ 2.7 kcal/mol) than that predicted after correction for the SE of cyclohexane (eq 16). Cyclization of the ester to afford δ-valerolactone suggests an SE of 10.2 kcal/mol, a value only a kcal/mol lower than that derived from a homodesmotic reaction (eq 19). The SE for δ-valerolactam, on the other hand, is a kcal/mol higher by the cyclization protocol. Hence, the general trend predicted by the two methods is mutually reinforcing and corroborates the suggestion that the SE of these six-member ring reference compounds are indeed *not* zero but still can provide a useful measure of the *relative* SE of the corresponding three- versus six-member ring systems containing the same functional group. We also emphasize that the cross referencing of the relative SE of varying functional groups with varying ring sizes in Figure 4 provides an especially informative “chart” to assess the SEs of these differing ring systems. From a pedagogical point of view, it is of interest to be able to estimate the relationships between the strain energies of different types of molecules of the same ring size.[6c] It is also useful to be able to predict the SE of interrelating compounds. For example, the insertion of a C═O into cyclopropane suggests that the SE of cyclobutanone is of a comparable magnitude (26.2 kcal/mol; see value in brackets, Figure 4).

Thus, the SE values on the diagonal in Figure 4 provide an estimate of the effect of the insertion of a functional group affording an entirely different functionality in the ring. With the exception of α-lactone, that is several kcal/mol too low, the predicted SEs of the three-member ring systems at the right of this chart are in excellent agreement with the SEs predicted by the several other methods, despite the fact that the final number is the result of three contiguous CH$_2$ extrusion reactions. This method also provides a reliable SE for the four-member ring compounds that are not as accessible by other means. This is especially true for the medicinally important β-lactam that has an estimated SE of 26.1 kcal/mol. It is also of interest that the five-member ring lactone, χ-lactone, has an SE that is 2.4 kcal/mol *less* than that of the six-member ring reference lactone.

We have also applied this procedure to estimate the SE of simple unsubstituted diaza compounds. The problems encountered above with the combination protocol demonstrate the utility of the insertion/expulsion method we describe above. For example, the energy equivalent for an α-N═N CH$_2$ group may be derived from the energy difference between *trans*-2-diazahexene (39.22811 au) and the β-CH$_2$ energy equivalent (39.22587 au) from one-half the energy difference between 3-diazahexene and 4-diazaoctene (Supporting Information). As noted by Wiberg,[23] the SE of diazacyclohexene is greater than that of diazacyclopentene, and we find a similar energy difference (Figure 5). If we assign, initially, a zero SE to diazacyclopentene, then the *relative* SE of diazacyclohexene is 6.6 kcal/mol. It is also of interest to note that the SE of diazacyclobutene is 5.0 kcal/mol greater than that of diazacyclopropene. However, in this case and that of the above assignments, we remain cognizant

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(23) Bobek, M. M.; Krois, D.; Brehmer, T. H.; Giester, G.; Wiberg, K. B.; Brinker, U. H. *J. Org. Chem.* **2003**, *68*, 2129.

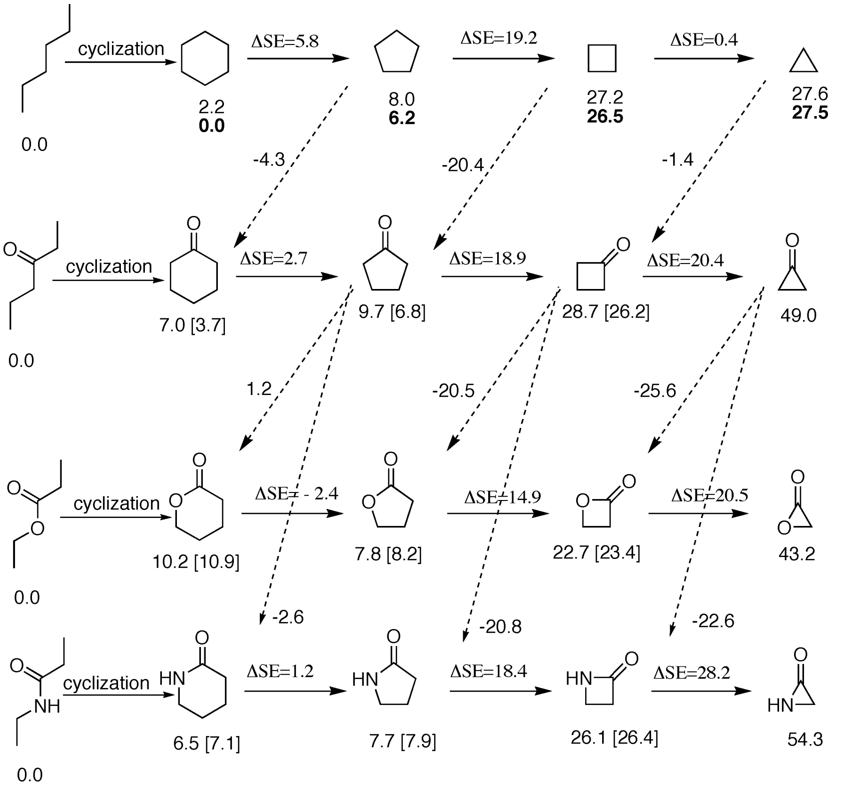

Figure 4. Strain energies (CBS-Q, kcal/mol) for the carbonyl derivatives based upon the insertion/extrusion of $-CH_2-$/$-O-$ energy equivalents. Relative energies (kcal/mol) of the six-member ring compounds are based upon the cyclization of acyclic all-*anti* reference molecules. The cyclization energy for *n*-hexane is calculated at the CBS-APNO level. The ΔSEs on the horizontal path (moving to the right) are derived from successive $-CH_2-$ extrusions from larger to smaller cyclic molecules. The SE values in brackets are estimated from the difference in the SE on the horizontal line and the energy of reaction for carbonyl, oxygen, and $-NH-$ insertion given on the dashed diagonal line. The plain SE numbers are based upon SE of the cyclized six-member compound plus the ΔSE on the horizontal path. The SEs in bold type are experimental values taken from ref 14. For these calculations, the following energy corrections have been used. ***Hydrocarbons:*** $E_{CH_2(RR)} = 39.22642$ au. ***Ketones:*** $E_{\alpha-CH_2} = 39.22611$ au, $E_{\beta-CH_2} = 39.22715$ au, $E_{C=O} = 113.19093$ au. ***Lactones:*** $E_{\alpha-CH_2} = 39.22631$ au, $E_{\beta-CH_2} = 39.22690$ au, $E_{-O-} = 75.15624$ au. ***Lactams:*** $E_{\alpha-CH_2} = 39.22579$ au, $E_{\beta-CH_2} = 39.22635$ au, $E_{-O-} = 55.28820$ au. Ring closure correction was calculated according to the formula $E_{corr} = 2E_{C-H} - E_{C-C} + 2E_H = 2(E_{CH_3CH_2CH_3} - E_{CH_3CH_2CH_2} - E_H) - (E_{n-hexane} - 2E_{CH_3CH_2CH_2}) + 2E_H = 1.175516$ au. For a more complete description, see ref 6c.

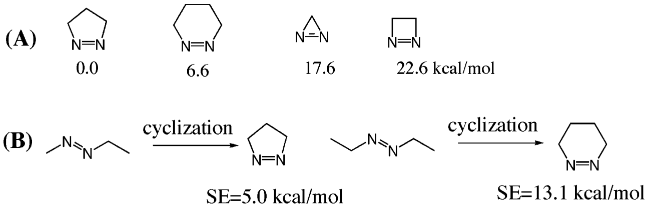

Figure 5. (A) Relative SEs (kcal/mol, CBS-Q) of cyclic diazo compounds calculated using α- and β-CH_2 energy equivalents (Table 3, last two rows). (B) SEs of diazacyclopentene and diazacyclohexene using the above cyclization protocol ($SE = E_{cyc} - E_{acyc} + E_{corr}$, $E_{corr} = 1.17552$ au).

of the fact that the linear reference compound still contains a N═N bond and the chemical reactivity of these compounds must be placed in perspective when discussing strain energies. However, cyclization of the *trans*-2,3-diazapentene reference compound to diazacyclopentene does suggest an SE of 5.0 kcal/mol. Consistent with this number, the SE of diazacyclohexene is estimated to be 13.1 kcal/mol with the *trans*-hexene reference alkene. This SE is comparable to the 11.1 kcal/mol estimated from the above homodesmotic reaction but would be reduced by 5.4 kcal/mol if calculated relative to the higher energy *cis*-diazaalkene reference compound as discussed above.

In this series of compounds, the SE of diazacyclopentene is also surprisingly low and is comparable to that in cyclopentene (SE = 6.2 kcal/mol).

4. Conclusions

(a) The strain energy (SE) of cyclohexane has been shown by several different methods to have the *nonzero* value of 2.2 kcal/mol. This suggests that the *conventional* strain energy of cyclopropane should be increased by one-half of this value to 28.6 kcal/mol (CBS-APNO).

(b) The strain energy of several relevant six-member reference molecules is also shown to have SE values that differ significantly from zero; the SEs of cyclohexanone (4.3 kcal/mol, G3), δ-valerolactone (11.3 kcal/mol), and δ-valerolactam (5.1 kcal/mol) provide a more accurate estimation of the SE of several key three-member ring compounds.

(c) After correction for the SE of the six-member reference compound, the SEs of cyclopropanone (49 kcal/mol), α-lactone (47 kcal/mol), and α-lactam **7** (55 kcal/mol) have been estimated on the basis of their combination with cyclopropane. These SEs have been shown to be in excellent agreement with those derived from well-balanced homodesmotic equations.

(d) An excellent correlation exists for the strain energy of small ring hydrocarbons and their C−H bond dissociation energies. This energy relationship does appear to hold for hetero-substituted compounds.

(e) The strain energies of three-member rings containing silicon are shown to increase, while those containing phosphorus and sulfur exhibit a comparable reduction in SE.

(f) The insertion of two heteroatoms (O−O, N=N, and O−N) into a three-member ring causes a marked reduction in strain energy.

Acknowledgment. This work was supported by the National Science Foundation (CHE-0138632), and partially supported by National Computational Science Alliance under CHE050085 and CHE050039N, and utilized the NCSA IBM P690 and NCSA Xeon Linux Supercluster.

Supporting Information Available: G3, CBS-Q, and CBS-APNO total energies. This material is available free of charge via the Internet at http://pubs.acs.org.

JA055086G