Effect of Geminal Substitution on the Strain Energy of Dioxiranes. Origin of the Low Ring Strain of Dimethyldioxirane†

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The strain energies (SE) for dioxirane (DO) dimethyldioxirane (DMDO) and related dioxiranes have been examined by several methods using high-level computational schemes (G2, G2(MP2), CBS-Q). A series of calculated O−O, C−O, and O−H bond dissociation energies (G2) point to special problems associated with classical homodesmotic reactions involving peroxides. The relative SEs of DO, DMDO, methyl(trifluoromethyl)dioxirane (TFDO), and difluorodioxirane (DFDO) have been estimated by combination of the dioxirane with cyclopropane to form the corresponding 1,3-dioxacyclohexane. The relative SE predicted for DMDO (**2**) is 7 kcal/mol lower than that of DO, while the SE of 1,1-difluorodioxirane (**4**) is 8 kcal/mol higher. The most reactive dioxirane, methyl (trifluoromethyl)dioxirane (**3**), has an estimated SE just 1 kcal/mol greater than that of DO but 8 kcal/mol greater than that of DMDO. Six independent methods support the proposed SE for DO of 18 kcal/mol. The SE of the parent dioxirane (DO) has been estimated relative to six-membered ring reference compounds by dimerization of dioxirane and or its combination with cyclopropane. The relative SE of cyclic hydrocarbons, ethers and peroxides have been predicted by the insertion/extrusion of $-CH_2-$ and $-O-$ fragments into their respective lower and next higher homologues. The moderated SE of DMDO (≈11 kcal/mol) has also been estimated on the basis of group equivalent reactions. The unusual thermodynamic stability of DMDO is largely a consequence of combined geminal dimethyl and dioxa substitution effects and its associated strong C−H bonds and $C-CH_3$ bonds. The data clearly demonstrate that the reference compounds used to estimate the SE for highly substituted small ring cyclic compounds should reflect their molecular architecture having the same substitutents on carbon.

Introduction

Early attempts to estimate strain energies of small cyclic compounds by Hehre et al.[1] used isodesmic reactions where the formal bonds were separated into the simplest molecules with the same bond type. Later, homodesmotic reactions[2] were introduced that attempted to more closely match the C−C bond types and the various types of C−H bonds on each side of the equation. The earliest homodesmotic equation to estimate the SE of cyclopropane (cyclopropane + 3 ethane = 3 propane)[2] predicts the SE of cyclopropane to be 27.3 kcal/mol (G2). This value is in excellent agreement with experiment (27.5 kcal/mol) despite the fact the bond dissociation energies (BDE) are poorly matched. The calculated (G2) bond energy for a C−H bond in cyclopropane is 108.8 kcal/mol, while the C−H bond energies in ethane (100.9 kcal/mol) and propane (101.5 and 98.5 kcal/mol) present an imbalance in favor of the left side of the above equation of −49.2 kcal/mol. Since the C−C bond energy in propane is 88.2 kcal/mol, the estimated C−C bond in cyclopropane would have to be about 80 kcal/mol in order for this equation to be energetically balanced and still have the left side of the equation 27.5 kcal/mol higher in energy. Such discrepancies in bond energies can have energetic consequences and can potentially influence the strain energy. This can be particularly true for cyclopropanes since Borden[3] has demonstrated that the major source of strain that results from the introduction of each trigonal (sp2) carbon center into a cyclopropane is not an increase in angle strain but the loss of a very strong cyclopropane C−H bond. A compilation of relevant G2 bond energies (ΔE_{total}) and bond dissociation energies (BDE = $\Delta H°_{298}$) is given in Table 1.

More recently, Bachrach[4] utilized group equivalent reactions that provide a more balanced homodesmotic equation. By an extension of the disproportionation reaction of Benson[5a] and the group separation reaction of Dill, Greenberg, and Liebman,[5b] an algorithm (eq 1) was suggested[4] that is homodesmotic and also conserves the chemical group equivalency. The two molecules of methanol and two molecules of ethanol balance the reaction and conserve equivalent groups. The success of this method, however, is strongly dependent upon the bond dissociation energies on both sides of the equation being nearly equivalent.

† Dedicated to Professor Waldemar Adam on the occasion of his 65th birthday.

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Table 1. Calculated O−O, C−O, O−H, and C−H Bond Energies (Δ*E*, kcal/mol) and Bond Dissociation Energies (BDE = Δ*H*°$_{298}$, kcal/mol) at the G2(MP2) and G2 Levels of Theory for Selected Characteristic Compounds Used in Homodesmotic Reactions (Numbers in the Last Column (BDE$_{exp}$, kcal/mol) Are Experimental)

	Bond type	ΔE (G2(MP2))	ΔE (G2)	BDE (G2) ΔH°$_{298}$	BDE$_{exp.}$
	O—O				
HO—OH	HO—OH	47.25	48.92	50.45	50.5[a]
CH_3O—OH	CO—OH	44.86	43.79	44.96	44.6[a]
CH_3O—OCH_3	CO—OC	39.98	38.73	39.43	37.8[a]
CH_3CH_2O—OCH_2CH_3	CO—OC	41.37	40.17		
CF_3O—OCF_3				47.50[b]	
H(C=O)O—OH	C(O)O—OH			47.95	
	C—O				
CH_3—OH	C—OH	92.23	91.55	93.60	
CH_3CH_2—OH	CC—OH	95.05	94.37	96.21	
$HOCH_2$—OH	(OH)C—OH	99.76	99.23	101.00	
CH_3—OCH_3	C—OC	84.26	83.40	85.13	
CH_3OCH_2O—CH_3	C—OC	79.85	78.99	80.42	
$HOC(CH_3)_2$—OH	C—OH	102.47	101.94	103.66	
CH_3OCH_2—OCH_3	OC—OC	82.84	84.52	85.45	
CH_3CH_2— OCH_2CH_3	CC—OC	88.21	87.34		
CH_3—OOH	C—OO	69.26	68.63	70.38	
CH_3—$OOCH_3$	C—OO	67.92	69.19	68.77	
CH_3CH_2—$OOCH_2CH_3$	CC—OO	70.81	70.02		
$HOOCH_2$—OOH	OC—OO	63.13	67.24	68.25	
	O—H				
CH_3O—H	CO—H	104.90	104.29	105.50	104.1[f]
CHF_2O—H	F2CO—H	115.80	115.38	116.64	
$HOCF_2O$—H	F2CO—H	116.01	115.58	116.83	
CHF_2OO—H	F2COO—H	90.98	90.56	91.80	
CH_3CH_2O—H	CO—H	105.28	104.71	104.60[c]	104.3[f]
HOCH2O—H	CO—H	111.69	108.12	109.64	
$HOC(CH_3)_2O$—H	CO—H	107.87	107.40	108.80	
HOO—H	OO—H	84.31	86.51	87.75	87.9[e]
CH_3OO—H	OO—H	85.46	86.99	86.21	
CH_3CH_2OO—H	OO—H	85.28	84.86		
	C—H				
cyclopropane	C—H	108.90	108.82	110.32	106.3[g]
cyclobutane	C—H	103.83	100.20	101.94	
cyclopentane	C—H	96.30	96.21	97.84	
dioxirane (DO)	C—H	102.28	102.26	103.73	
dimethyldioxirane (DMDO)	C—H	101.01		102.65[d]	
1,2-dioxacyclobutane	C—H	102.42	102.43	103.73	
1,2-dioxacyclopentane	α-C—H	95.61		96.62[d]	
1,2-dioxacyclopentane	β-C—H	100.76		102.35[d]	
CH_3CH_2OH	α-C—H			94.9[c]	
CH_3CH_2OH	β-C—H			101.9[c]	
$HOCH_2$—H	OOC—H	98.4	98.3	99.9	
$HOCF_2$—H	OO(F2)C—H	105.8	105.7		
$HOC(CH_3)_2$—H	OO(CH3)2C—H	96.39	96.56		
$CH_3OOCH_2CH_2$—H	β-C—H(ROOR)	102.70	102.63		
$CH_3CH_2OCH_2CH_2$—H	β-C—H(ROR)	102.51	102.45		
CH_3—H	C—H	104.01	104.04	105.80	
CH_3CH_2—H	CC—H	100.91	100.85	102.62	98.2[g]
CH_3CH_2 CH_2—H	1° C—H	101.54	101.51	103.26	101.0[h]
CH_3(HC—H)CH_3	2° C—H	98.59	98.47	100.28	99.1[h],98.6[i]
CH_3OOCH_2—H	OOC—H	97.99	97.93	99.40	
$CH_3CH_2OCH_2$—H	OC—H	96.23	96.20		
$CH_3CH_2OCH_2CH_2CH_2$—H	γ-C—H(ROR)	101.35			
CH_3CF_2—H	F2C—H	101.01	100.92	102.46	
	C—C				
CH_3—CH_3	C—C	88.55	88.30	90.8	90.4[g]
CH_3CH_2—CH_3	C-CC	88.51	88.19	90.46	85.8[g], 88.2[h]
CH_3CH_2—CH_2CH_3	CC—CC	88.73	88.39		
$CH_3CH_2CH_2$—$CH_2CH_2CH_3$	CC—CC	90.61	90.35		
$CH_3CH_2OCH_2$—CH_3	OC—C	87.05	86.80		
	C—CO	97.33	97.08	98.93	
$(OH)_2C(CH_3)$—CH_3	OC—C	91.13	90.86	92.90	
$CH_3CH_2OCH_2CH_2$—CH_3	β-C—C(ROR)	90.17			

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$$\overbrace{(CH_2)_{n-1}-O}^{} + (n-2)\,CH_3CH_3 + 2CH_3OH \rightarrow CH_3OCH_3 + (n-3)CH_3CH_2CH_3 + 2CH_3CH_2OH \quad (1)$$

Equation 1 gave strain energies that were systematically *higher* than those that simply used homodesmotic reactions that do not always conserve the next nearest neighbor concept as demonstrated in eq 2.[2] This homodesmotic reaction for determining the SE of cyclooxaparaffins has two carbons bound to one C, one O, and two H atoms but no such carbon is present on the right side of eq 2.

$$\overbrace{(CH_2)_{n-1}-O}^{} + nCH_3CH_3 \rightarrow CH_3OCH_3 + (n-1)CH_3CH_2CH_3 \quad (2)$$

In recent years, cyclic peroxides such as dimethydioxirane (**2**) (DMDO) and methyl(trifluoromethyl)dioxirane (**3**) (TFDO) have found increasing utility as oxidizing agents for heterocyclics, alkenes, and saturated hydrocarbons.[6] The reactivity of dioxiranes as oxygen atom donors has been ascribed largely to their strain energy (SE). The *presumed* high rates of epoxidation by three-membered ring peroxides have been attributed to a driving force for O transfer due to the relief of ring strain and the favorable enthalpy change attending the formation of a strong C=O π-bond. The even greater reactivity of TFDO (≥1000-fold) compared to DMDO has been imput additionally to the inductive effect of the CF_3 substitutent on the dioxirane ring.[6a,b] However, the "legendary" reactivity of dioxiranes, as a class of oxidant, was divined in the early literature due simply to the fact that these cyclic peroxides could readily oxidize saturated hydrocarbons even at low temperatures, a level of reactivity not enjoyed by other oxidizing agents such as peracids. While the reactivity of DMDO in the epoxidation reaction is generally considered to be at least equal to or even greater than that of a peracid,[6,7] our theoretical data[8] suggest that the gas-phase intrinsic oxygen atom donor propensities of these two classes of reagents are essentially comparable. Experimental rate data estimates[6b] suggest that the reactivity of DMDO toward alkenes exceeds that of a typical peracid, peroxybenzoic acid (PBA), by a factor ranging up to 10^2. However, the observed rate ratio for DMDO versus PBA in solution ($k_{DMDO}/k_{PBA} = 74$)[6b] can also be attributed to well-established solvent and hydrogen-bonding effects that increase the rate of DMDO epoxidation.[7] This level of *predicted* reactivity for DMDO is not consistent with what has been generally anticipated for a highly strained cyclic peroxide.

The SE of the parent dioxirane DO (**1**) was recently revised downward from 32.8 to 26.4 kcal/mol at the CCSD(T) level based upon an updated heat of formation $\Delta H_{f(298)}$ for DO.[9a,b] While the SE of DO is more of academic interest, the SE of the most widely used dioxirane, DMDO, is of general interest to the experimentalist. We have several lower estimates for the SE of both DO (**1**) and DMDO (**2**) that are more consistent with our theoretical predictions of dioxirane reactivity toward alkenes.

Computational Methods

Ab initio molecular orbital calculations[10] were performed with the Gaussian 98 system of programs.[11] The Becke three-parameter hybrid functional[12a,13a] combined with the Lee, Yang, and Parr (LYP) correlation functional,[12b] denoted B3LYP,[13b] was employed in selected calculations using density functional theory (DFT). Geometries were optimized[14] at the B3LYP and QCISD levels using the 6-31G* and 6-311+G(3df,-2p) basis sets (the latter was used only for the B3LYP optimizations). The reaction enthalpies and strain energies were calculated using G2 and in some cases G2(MP2) theory.[15] Selected formal reactions were calculated at the CBS-Q and CBS-APNO levels.[11,15d] While the G2 method may potentially not be ideally suitable for all peroxides since the geometries are optimized with a relatively small basis set (MP2/6-31G*),[9b] it does provide an internally consistent set of G2 energies for the comparison of the strain energies of cyclic peroxides with other small ring compounds. Zero-point energies (ZPE) and thermal corrections to obtain reaction enthalpies at 298 K in the G2 series are computed by convention at the HF/6-31G* level. All references compounds quoted are true minima as established by a frequency calculation. The C_s and C_{2v} reference compounds were optimized without geometry constraint.

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(8) The QCISD(T)//QCISD/6-31G(d) classical barriers for the epoxidation of E−2-butene with peroxyformic acid and DMDO are 13.5 and 14.6 kcal/mol. These barriers at QCISD(T)/6-31G(d)//B3lYP/6-311+G-(3df,2p) are 13.2 and 14.3 kcal/mol.

(9) (a) With a $\Delta H_{f(298)}$ derived from the experimental heat of formation of formic acid (−90.60 kcal/mol) and a calculated $\Delta H_{(298)} = -90.44$ between formic acid and DO (G2), the $\Delta H_{f(298)}$ for dioxirane (−0.2 kcal/mol) at the G2 level is in excellent agreement with the value suggested by Cremer ($\Delta H_{f(298)} = -0.3$ kcal/mol)[6b] at the CCSD level. The $\Delta H_{f(298)}$ of DO derived from atomization energies at the G2 level is −2.07 kcal/mol. (b) Cremer, D.; Kraka, E.; Szalay, P. G. *Chem. Phys. Lett.* **1998**, *292*, 97. (c) Palyk, A.; Sander, W.; Gauss, J.; Cremer, D. *Angew. Chem.* **1989**, *101*, 920. (d) Although it has been suggested[6b] that f orbitals are required to get accurate O−O bond distances in certain peroxides, our data suggest that the larger basis set has a greater influence on the relative total energies of the isomeric peroxides than on the geometry.

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Table 2. Strain Energies (kcal/mol, G2) Based upon Group Equivalent Homodesmotic Reactions (Experimental SEs Are Taken from Ref 22 and Are Given in Bold Type)

Substituent X				
—CH_2—	0.2[a]	6.4	25.7	27.3
	0.0	**6.2**	**26.5**	**27.5**
—O—	1.2[b]	5.7	24.9	26.4
	0.0	**5.4**	**24.7**	**26.3**
	1.1[c]	6.1	25.4	27.0
	0.0	**5.8**	**25.2**	**26.7**
				
	5	**24**	**25**	**1**
	2.2[d]	5.6	26.7	19.1[e]

[a] Strain energies are computed using the equation $(CH2)_n + nCH_3CH_3 \rightarrow nCH_3CH_2CH_3$ and G2 total energies. [b] Strain energies are computed using eq 1. [c] Strain energy computed using eq 1 with the corresponding analogous secondary amines (G2(MP2)). [d] Strain energies derived from an adaptation of eq 1 as demonstrated by the balanced reaction 1,2-dioxane + $3CH_3CH_3$ + $2CH_3OH = CH_3OOCH_3$ + $2CH_3CH_2CH_3$ + $2CH_3CH_2OH$. [e] SE derived from the following equation: dioxirane + HOOH + $2CH_3OH = 2CH_3OOH + CH_2(OH)_2$ using the planar diol (see ref 17a).

All energy values quoted in the text are at the G2 level unless specified otherwise.

Results and Discussion

Ring Strain Energy of Dioxiranes from Homodesmotic Reactions. Homodesmotic reactions have played a major role in assessing the energetics of a wide variety of chemical transformations for more than 25 years.[2] Computational efficiency has now progressed to the point where we can also examine such balanced reactions more closely by calculating bond dissociation energies (BDE) at the G2 level to within 1−2 kcal/mol. Examination of the calculated BDE (Table 1) for the O−O, C−O, and O−H bonds in ethers versus peroxides, however, clearly points to potential problems in accurately balancing the energies of homodesmotic reactions involving peroxides. For example, the O−O BDE for even simple peroxides differ by as much as 10 kcal/mol. The O−H versus OO−H bonds in simple alcohols versus hydroperoxides can differ by about 20 kcal/mol and the C−O versus C−OO bonds by as much as 25 kcal/mol. This can present problems when writing balanced reactions based simply upon balanced functional groups that may be used to predict even the relative strain energy of cyclic ethers versus peroxides. This is especially true when the group equivalent method[4] is extended to peroxides and the OH functional group is used as in eq 1. The algorithm in eq 1, when applied to three-membered ring peroxides (dioxiranes), is further complicated by the use of a geminal diol reference molecule with its attending energetic problems associated with the anomeric effect.[16] An essential feature of any method used to determine accurately the SE of small ring compounds requires an exact balance of the molecular architecture on both sides of the equation. As we shall demonstrate, this has proven to be especially true for DMDO where the dioxa and dimethyl substitution pattern of its tetrahedral carbon atom *each* exert a significant stabilizing influence and must be duplicated on both sides of the equation.

We get excellent agreement with experiment for alkanes, ethers and amines using the group equivalent modification[4] of homodesmotic equations[2] as shown in eq 1 (see Table 2). However, we continue to experience problems with using geminal diols as reference compounds as delineated below.

Our initial assessment of the strain energy of dioxirane (DO) used the same homodesmotic reaction reported earlier by Cremer (eq 3),[9] suggesting an SE = 26.4 kcal/mol at the CCSD(T) level.[9b] However, this equation has several unbalanced bond energies. For example, the C−O BDE in CH_3−OH is 24.8 kcal/mol greater than the C−O bond in CH_3−OOH (Table 1). Additionally, the use of the $\Delta H_{f(298)}$ of methanediol as a reference compound in its equilibrium C_{2v} geometry raises several questions. The use of such homodesmotic equations for the energetics of hydrocarbon reactions is well established, but their extension to 1,3-dioxa reference molecules remains cryptic. Can $HOCH_2OH$ potentially introduce an error due to intramolecular hydrogen bonding that can lower its ground-state energy thereby increasing the calculated strain energy? Does the 1,3-arrangement of lone pairs of electrons in methanediol, with the two OH hydrogens anti-positioned and its lone pairs of electrons skewed,[17a] serve as a good model for DO where the lone pairs are eclipsed?

At the G2 level, the SE of dioxirane based upon homodesmotic reaction 3 is calculated to be 19.1 kcal/mol using the all-anti planar C_s structure. The O−H

(16) (a) Corttes, F.; Tenorio, J.; Collervao, O.; Cuevas, G *J. Org. Chem.* **2001**, *66*, 2918. (b) Alabugin I. V. *J. Org. Chem.* **2000**, *65*, 3910. (c) Kneisler, J. R.; Allinger, N. L. *J. Comput. Chem.* **1996**, *17*, 757.

(17) (a) We have located three stationary points for methanediol. A structure with the hydrogens anti (C_{2v}), one with the hydrogens syn and a C_s structure (a first-order saddle point) having relative energies (G2) of 0.0, 2.31 and 6.38 kcal/mol. (b) 2,2-Propanediol has similar relative energies: 0, 2.72, and 6.29 kcal/mol for the C_{2v}, structure, one with the hydrogens syn and the C_s structure. (c) The C_s minimum of $HOCF_2OH$ is 1.17 kcal/mol lower in energy [MP2(Full)/6-31G(d)] than the C_{2v} structure.

BDEs for CH_3O-H and $HOCH_2O-H$ differ by 4 kcal/mol favoring the *gem*-diol. As noted previously, the C−O BDEs also differ widely. The calculated SE is 25.5 kcal/mol using the lowest energy minimum located for $CH_2(OH)_2$.[17a] This difference in predicted SE is due solely to the energy difference (6.4 kcal/mol) between $HOCH_2OH$ in its planar eclipsed arrangement versus the skewed C_{2v} global minimum.[17a] Thus, due to both bond energy differences and the anomeric effect, the use of homodesmotic reactions for dioxiranes is problematic. Consequently, we have cautiously used a planar conformation for methanediol (C_s)[17a] and related structures as reference compounds.

In an effort to eliminate potential intramolecular hydrogen bonding interactions associated with $CH_2(OH)_2$, we used the planar all-anti dimethyl ether $CH_3OCH_2OCH_3$ (eq 4) and also predict an SE = 18.9 kcal/mol for DO. This equation appears to have the best group equivalent balance since the C−O bonds in the ether reference molecule differ by only 1 kcal/mol (Table 1). As shall become evident, we do get consistently lower predicted SE, in better agreement with the several other methods described, if we use the C_s *gem*-diol or dimethyl ether.

$$DO + 2CH_3OH + HOOH \rightarrow CH_2(OH)_2 + 2CH_3OOH \quad -19.1 \text{ kcal/mol} \quad (3)$$

$$DO + 2CH_3OCH_3 + HOOH \rightarrow CH_3OCH_2OCH_3 + 2CH_3OOH \quad -18.9 \text{ kcal/mol} \quad (4)$$

$$DO + 2CH_3OH \rightarrow CH_2(OH)_2 + CH_3OOCH_3 \quad -19.2 \text{ kcal/mol} \quad (5)$$

$$DO + 2CH_3OCH_3 \rightarrow CH_3OCH_2OCH_3 + CH_3OOCH_3 \quad -19.0 \text{ kcal/mol} \quad (6)$$

Replacement of HOOH with CH_3OOCH_3 in eq 5 provides a better balance of functional group equivalents for the $-CH_2OO-$ fragment in DO. Using the calculated $\Delta H_{f(298)}$ for dioxirane (−0.2 kcal/mol)[9a] and experimental[18a] values for CH_3OCH_3 (−43.99 kcal/mol) and $CH_3OCH_2OCH_3$ (−83.21 kcal/mol), the SE for DO remains quite high at 25.0 kcal/mol. The C−O BDE in CH_3O-CH_3 is 4.7 kcal/mol stronger than the CH_3-O bond in $CH_3OCH_2OCH_3$. Despite the appearance of balance of bond types on both sides of the equation, the environment of the oxygen lone pairs has apparently not been maintained. The C_{2v} minimum for $CH_3OCH_2OCH_3$ is 6.4 kcal/ml more stable than the planar C_s stationary point (with eclipsed oxygen lone pairs), and the experimental $\Delta H_{f(298)}$ is obviously derived from this minimum energy conformation.[17a] Problems of this nature simply do not arise when applying homodesmotic reactions to hydrocarbon reactions.

When eq 3 is adapted to DMDO, an SE of 14.7 is suggested, a value that is 4.4 kcal/mol lower than that of DO (eq 7). The SE for DMDO is further reduced to 10 kcal/mol when the dimethyl ether of 2,2-propanediol is used as the reference compound[17b] in eqs 8 and 9. The approximate C_{2v} conformer of reference molecule $(CH_3O)_2C(CH3)_2$ is 7.6 kcal/mol more stable than the C_s conformer (Table S1).

$$DMDO + 2CH_3OH + HOOH \rightarrow (CH_3)_2C(OH)_2 + 2CH_3OOH \quad -14.7 \text{ kcal/mol} \quad (7)$$

$$DMDO + 2CH_3OCH_3 + HOOH \rightarrow (CH_3O)_2C(CH_3)_2 + 2CH_3OOH \quad -10.1 \text{ kcal/mol} \quad (8)$$

$$DMDO + 2CH_3OCH_3 \rightarrow (CH_3O)_2C(CH_3)_2 + CH_3OOCH_3 \quad -10.2 \text{ kcal/mol} \quad (9)$$

Extending eq 3 to difluorodioxirane (**4**) (DFDO), where the difluoro substitution pattern present in all four participants is balanced on both sides of the equation (eq 10), affords a calculated SE for DFDO of 20.9 kcal/mol at the G2 level of theory in excellent accord with the most recent prediction of 20.8 kcal/mol.[9b] In this case, both the C_{2v} and the planar C_s minima of HOCF2OH have comparable energies.[17c]

$$DFDO + HOOH + 2CHF_2OH \rightarrow 2CHF_2OOH + CF_2(OH)_2 \quad -20.9 \text{ kcal/mol} \quad (10)$$

$$DFDO + 2HCF_2OCH_3 \rightarrow CH_3OCF_2OCH_3 + HCF_2OOCF_2H \quad 20.7 \text{ kcal/mol} \quad (11)$$

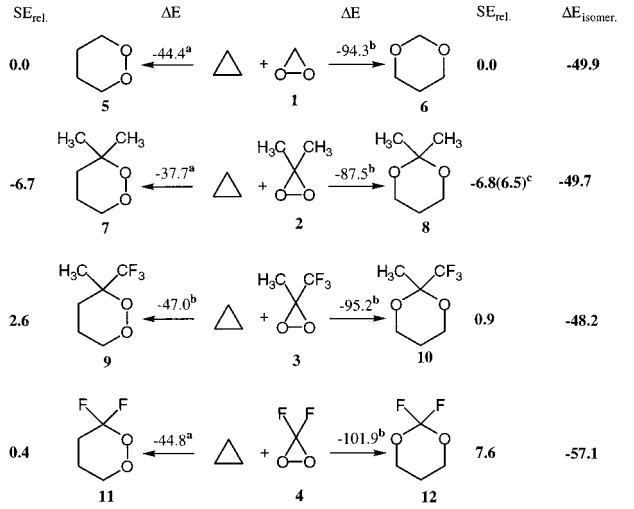
Homodesmotic reaction 11 also suggests that the SE of DFDO is 21 kcal/mol. In this case, the diether reference compound $CH_3OCF_2OCH_3$ exists as the global minimum in its C_s conformation.

Strain Energies Derived from the Dimerization of Three-Membered Rings. The above concerns prompted us to devise methods to determine the *relative* SE of the basic series of dioxiranes that are not dependent upon balancing exactly a homodesmotic reaction. We initiated this part of the study with an extension of the dimerization (diagonal) method reported by Liebman and co-workers a number of years ago.[19] Combination of the parent dioxirane DO with cyclopropane, in two different orientations, formed cyclic peroxide, 1,2-dioxacyclohexane (**5**) and 1,3-dioxacyclohexane (**6**) (Table 3). The former orientation preserves the peroxide functionality that offers energetic advantages of maintaining this difficult functionality on both sides of the equation. The latter combination cleaves the O−O bond but preserves the group equivalency of the essential $O-CH_2-O$ functionality. The reaction energies differ significantly (49.9 kcal/mol) due to the retention of the high energy peroxide bond in **5**. Combination of DMDO with cyclopropane in a similar manner gives a nearly identical energy *difference* in the 1,2- and 1,3-dioxa-isomers (49.7 kcal/mol) suggesting a net cancellation of bond energy differences (BDEs) for the two six-membered ring reference compounds (**7** and **8**) despite the lack of group balance in **7**. The requisite tetrahedral, dioxa, dimethyl substitution pattern in 1,3-dioxa-2,2-dimethylcyclohexane (**8**) has been maintained. The reaction energies (ΔE) for these two

(18) (a) NIST *Standard Reference Database*, No. 69, Nov 1998 (http://webbook.nist.gov/chemistry.) (b) The calculated $\Delta H_{f(298)}$ for DMDO (−26.1 kcal/mol), and experimental heats of formation[18a] for CH_3OH (−48.0 kcal/mol), $HOCH_2CH_2CH_2OH$ (−97.61 kcal/mol), CH_3OOCH_3 (−30.0 kcal/mol) give a SE for DMDO of 5.5 kcal/mol (DMDO + $2CH_3OH = CH_3OOCH_3 + HOCH_2CH_2CH_2OH$) relative to an unbranched reference compound

(19) For earlier examples of this dimerization (diagonal)[18b] approach, see: (a) Van Vechten, D.; Liebman, J. F. *Isr. J. Chem.* **1981**, *21*, 105. (b) Skancke, A.; Van Vechten, D.; Liebman, J. F.; Skancke, P. N. *J. Mol. Struct.* **1996**, *376*, 461 and references therein. (c) Liebman, J. F.; Skancke, P. N. *Int. J. Quantum Chem.* **1996**, *58*, 707. (d) Zeiger, D. N.; Liebman, J. F. *J. Mol. Struct.* **2000**, *556*, 83.

Table 3. Relative Strain Energies (kcal/mol) Based upon the Reaction Energy for the Combination of Cyclopropane with Dioxiranes To Form Six-Membered Ring Reference Compounds



[a] G2(MP2). [b] CBS-Q. [c] CBS-APNO.

reactions establishes the relief of ring strain for DMDO to be 6.8 kcal/mol *less* than that of DO.

Combination of methyl(trifluoromethyl)dioxirane (TFDO) with cyclopropane suggests a relative SE difference with DO of only 0.9 kcal/mol based upon the 1,3-adduct **10**. Significantly, the relative SE of TFDO is 7.7 kcal/mol greater than that of DMDO consistent with its much greater reactivity as an oxygen atom donor. The greater reactivity of TFDO (≥1000-fold) compared to DMDO has been imputed largely to the inductive effect of the CF_3 substitutent on the dioxirane ring.[6]

The SE of difluorodioxirane (DFDO) is 7.6 kcal/mol relative to its parent DO. This estimate is clearly at odds with homodesmotic reactions 10 and 11 where the SE (21 kcal/mol) is predicted to be only 2 kcal/mol greater than that of DO. The SE based upon the dimerization to 1,3-isomer **12** is significantly higher than that predicted by dimerization to cyclic peroxide **11**. In general, geminal CF_2 substitution has a far greater influence on adjacent bond energies than dialkyl substitution.[20] Indeed, DFDO has a predicted strain energy that is 14 kcal/mol greater than that of DMDO.

Since the anomeric effect can potentially have large energetic consequences that are dependent upon the orientation of the oxygen lone pairs, we have also used a series of acyclic formal reactions that provide an equivalent assessment of the relative SEs of these dioxiranes. Each side of formal reaction 12 is exactly balanced with a dimethyl ether that preserves the geometry at the dioxirane carbon. When both methyl ethers are in their global minimum C_{2v} conformations, the relative SE for DMDO is 6.8 kcal/mol lower; a value identical to that based upon the above dimerization protocol. That energy increases only slightly to 7.7 kcal/mol when the C_s reference compounds are used. A comparison of the relative SE of DO with DFDO is also provided by eq 13.

$$DO + (CH_3O)_2C(CH3)_2 \rightarrow DMDO + CH_3OCH_2OCH_3 \quad -6.8 \text{ kcal/mol } (C_{2v}) \quad (12)$$

$$DFDO + CH_3OCH_2OCH_3 \rightarrow DO + CH_3OCF_2OCH_3 \quad -7.6 \text{ kcal/mol} \quad (13)$$

$$DFDO + (CH_3O)_2C(CH_3)_2 \rightarrow DMDO + CH_3OCF_2OCH_3 \quad -14.4 \text{ kcal/mol} \quad (14)$$

With both reference compounds as global minima and preserving the group equivalency, we again get an identical energy match with the above dimerization method (Table 3). Formal reaction 14 corroborates the above prediction that the SE of DFDO is 14 kcal/mol greater than that of DMDO. Thus, the inherent SEs of these three dioxiranes are in remarkable agreement with the above dimerization protocol (Table 3) just as long as the tetrahedral carbon environment of each dioxirane is maintained throughout. We suggest that this combination method provides more reliable *relative* SEs for this series of dioxiranes than the above homodesmotic reactions.

Extension of this dimerization (diagonal)[19] protocol to determine the absolute SE of several small rings compounds with known experimental SEs provides a check on the above *relative* dioxirane data. The dimerization of cyclopropane affords a larger relatively strain-free molecule, cyclohexane that differs only in the bond angles of the fragments and the number of gauche interactions. Based upon the differences in computed total energies, that include zero-point energy corrections, the dimerization of cyclopropane, where $SE = (2E_{\text{cyclopropane}} - E_{\text{cyclohexane}})/2$, gives an SE = 27.2 kcal/mol at the G2 level of theory and 27.1 kcal/mol at the G2(MP2) level (Table 4).[21a]

We also estimate the strain energy of ethylene oxide. Dimerization of oxirane (**13**) to afford 1,4-dioxane (**14**) gives an $SE = (2E_{\text{oxirane}} - E_{\text{dioxane}})/2$ = 24.6 kcal/mol at both the G2 and G2(MP2) levels of theory (Table 4).[19b] A comparable SE (25.4 kcal/mol) for oxirane is derived from its combination with cyclopropane to give tetrahydropyran (**15**).

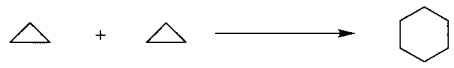
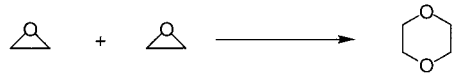
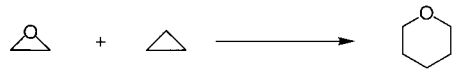
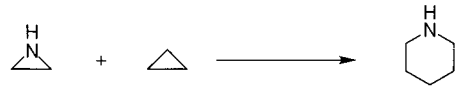
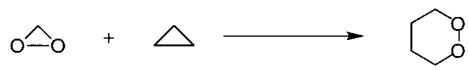
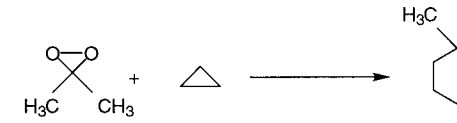
Estimates of the SE of aziridine **16** (SE = 26.2 kcal/mol, G2(MP2)) and ethylene sulfide **18** (18.9 kcal/mol, G2(MP2)) are also given relative to their corresponding six-membered ring reference compounds (Table 4). The reduced SE for the latter thio derivative of oxirane was anticipated on the basis of the larger heteroatom and a longer C−S bond distance (1.814 Å). The inclusion of two heteroatoms in a three-membered ring tends to reduce the SE and the strain energy for the simplest oxaziridine **20** is predicted to be only 18.8 kcal/mol (G2(MP2)) based upon reference compound **21**.

These data suggest that this dimerization protocol could also provide reasonable estimates of the strain energies of the dioxiranes relative to their six-membered ring reference compounds. Dimerization of the parent dioxirane **1** to afford s-tetroxane **22** (1,2,4,5-tetraoxacy-

(20) For a thorough discussion of the energetic consequences of geminal difluoro substitution, see: (a) Getty, S. J.; Hrovat, D. A.; Xu, J. D.; Barker, S. A.; Borden W. T. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1689. (b) Wiberg, K. B.; Marquez, M. *J. Am Chem. Soc.* **1998**, *120*, 2932.

(21) (a) From the experimental $\Delta H_{f(298)}$ for cyclopropane (12.74 kcal/mol) and cyclohexane (−29.43 kcal/mol),[18a] the SE for cyclopropane (27.46 kcal/mol) is in excellent agreement with experiment (27.5 kcal/mol).[22] (b) Based upon the experimental $\Delta H_{f(298)}$ for oxirane **13** of −12.58 kcal/mol, and a $\Delta H_{f(298)} = -75.36$ kcal/mol for 1,4-dioxane **14**,[18a] dimerization of oxirane to 1,4-dioxane gives an experimental SE for oxirane (**13**) of 25.1 kcal/mol in good agreement with experimental data (26.3 kcal/mol).[6]

Table 4. Three-Membered Ring Strain Energies (SE, kcal/mol) Derived from Dimerization to Six-Membered Ring Reference Compounds (Experimental SE Values (SE_{exp}, kcal/mol) Are Given in the Last Column for Comparison)

Reaction	SE G2(MP2)	$SE_{exp.}$
	27.1 (27.2)[a]	27.5
 **13** **13** **14**	24.6 (24.6)[a]	26.3
 **13** **15**	25.4[b] (25.3)[a]	26.3
 **16** **17**	26.2	26.7
 **18** **19**	18.9	
 **20** **21**	18.8	
 **1** **1** **22**	19.6	
 **1** **5**	17.3 (16.9)[a]	
 **2** **7**	10.6	

[a] The SE given in parentheses are at the G2 level. [b] The total SE for this reaction (52.5 kcal/mol) and those that follow are corrected for the SE of cyclopropane (27.1 kcal/mol); SE = $[(E_{THP} - (E_{oxirane} + E_{cyclopropane}))627.51 - 27.1]$ (kcal/mol).

clohexane)[23] suggests a relatively low strain energy for DO, SE = 19.6 kcal/mol (G2(MP2)). However, the accuracy of this estimate is dependent upon the SE of the tetraoxa reference molecule **22**. Hydrogenation of **22** to two CH_3OOH molecules (see below) suggests an SE of 2.2 kcal/mol and consequently an estimated SE for DO of only 17 kcal/mol relative to an acyclic reference compound. Combination of **1** with cyclopropane affording cyclic reference compound 1,2-dioxane **5** predicts an SE = $(E_1 + E_{cyclopropane}) - E_5$ = 16.9 kcal/mol; however, the group equivalency is not as well balanced. Similarily, combination of DMDO **2** with cyclopropane to afford 3,3-dimethyl-1,2-dioxacyclohexane (**6**) suggests the low SE of 10.6 kcal/mol, a value in excellent accord with the above relative SE (Table 1) where the SE of DMDO is predicted to be 6.8 kcal/mol lower than that of DO. However, this predicted SE is with respect to a gem-dimethyl substituted reference compound where the group equivalency has not been as well balanced. The predicted strain energies calculated thus far for these three dioxiranes, based upon this dimerization protocol, suggests that the relative stability's of DO (SE = 15−19 kcal/mol) and TFDO are comparable but that DFDO has a strain energy that is 7 kcal/mol greater. The *gem*-dimethyl substitutents of DMDO (SE ≈11 kcal/mol) provides the same stabilization of 6−10 kcal/mol noted with cyclopropanes and other small ring compounds.[24a] Since the dogma surrounding the reactivity of DMDO is based upon its presumed strain energy, these relatively

(22) For recent discussions of strain energies, see: (a) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 4450. (b) Alcami, M. Mo. O.; Yanez, M. *J. Compt. Chem.* **1998**, *19*, 1072 and references therein. (c) Cremer, D.; Kraka, E. In *Theoretical Models of of Chemical Bond*; Maksic, Z. B., Ed.; Springer: Heidelberg, 1990; Vol. 2, p 453. (d) Wiberg, K. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312. (e) Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic Press: New York, 1978.

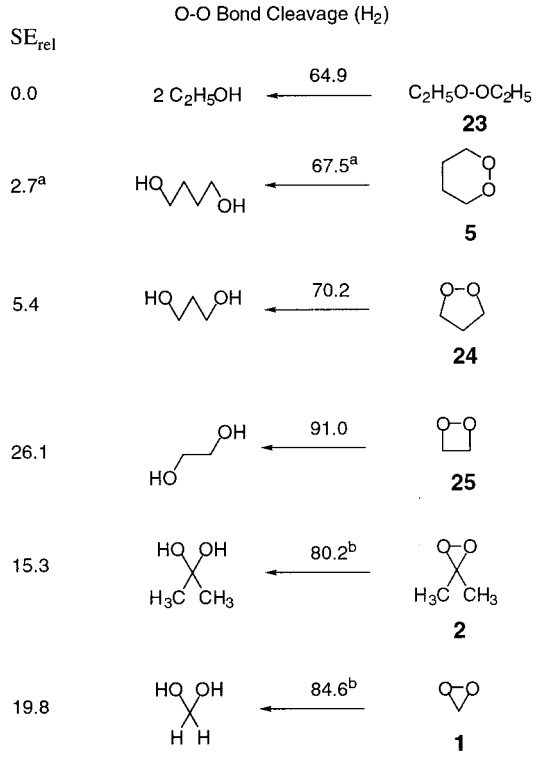
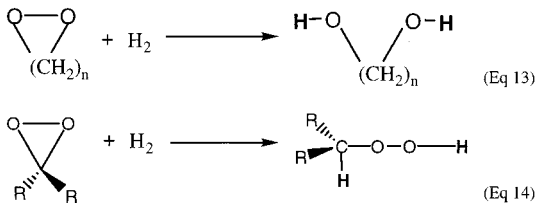


Figure 1. Energies of hydrogenation (ΔE, kcal/mol) of cyclic peroxides and strain energies (SE_{rel}, kcal/mol) relative to the acyclic reference compound, diethyl peroxide, at the G2 level of theory. Key: (a) G2(MP2); (b) the energy is calculated using the constrained C_s geometry of the diol reference compound.

low predicted SE will be *independently* corroborated by additional methods.

Relative Stability of Peroxides Based upon Hydrogenation Energies. Another qualitative measure of the *relative* stability of this series of dioxiranes can potentially be gleaned from the energies of hydrogenation of their O−O and C−O bonds to the corresponding diols and alkyl hydroperoxides (Figure 1).



In a similar fashion, the hydrogenation of the carbon−carbon double bond has traditionally served to establish the thermodynamic stability of substituted alkenes by reduction to their corresponding alkanes. The G2 energy of hydrogenation of diethyl peroxide (**23**) to two ethanol molecules ($\Delta E = -64.9$ kcal/mol) can be taken as a typical reference ΔE_{hyd} value for an acyclic peroxide. The $\Delta\Delta E_{hyd} = 2.7$ kcal/mol (G2(MP2)) for the hydrogenation of diethyl peroxide versus 1,2-dioxane **5** provides an estimate of its SE. The $\Delta\Delta E_{hyd} = 5.4$ kcal/mol for 1,2-dioxolane **24** is in excellent agreement with other estimates of their *relative* strain energies (Table 5). The SE of 1,2-dioxetane **25** ($\Delta\Delta E_{hyd} = 26.1$kcal/mol) relative to 1,2-dioxane **5** determined by this hydrogenation scheme is also in quite good accord with those summarized in Table 5. The SEs for DO and DMDO by this method are 19.8 and 15.3 kcal/mol, a difference of only 4.5 kcal/mol (see also eqs 7 and 8). In this case, the O−H BDEs for the two geminal diols differ by 0.8 kcal/mol. As noted above, both diols are in their C_s conformation.

The problems with the *gem*-diol reference compounds can be ameliorated in part by using the hydrogenation energies for reduction of the C−O bond provided that the newly formed C−H bonds (eq 24) have comparable bond energies (see Table 1). For the reaction DO + H_2 → CH_3-OOH, the predicted SE for DO is 16.3 kcal/mol while that for DMDO is 7.2 kcal/mol. Since the tertiary C−H bond derived from DMDO $(CH_3)_2CHOOH$ is 2.0 kcal/mol weaker than that resulting from reduction of DO (Table 1), the corrected SE = 9 kcal/mol for DMDO is quite consistent with the DSE of 7 kcal/mol noted above. The predicted SE for dioxetane **25** (26.1 kcal/mol) suggests a SE approximately 11 kcal/mol greater than that of DO in excellent agreement with the estimate below based upon $-CH_2-$ insertion. A more complete compilation of C−O hydrogenation products is given in Figure S1 (Supporting Information).

The SE of s-tetroxane **22** (1,2,4,5-tetraoxacyclohexane) presents a special case since both CH_2 groups are flanked by an O−O group. Hydrogenation of **22** affording two CH_3OOH molecules is attended by the liberation of 15.4 kcal/mol. We therefore used the minimum energy conformation of $HOOCH_2OOH$ as the acyclic reference instead of diethyl peroxide. The $\Delta E_{hyd} = -13.2$ kcal/mol for the reaction $HOOCH_2OOH + H_2 \rightarrow CH_3OOH + HOOH$ suggests that cyclic diperoxide **22** is only slightly strained (2.2 kcal/mol). The OOC−OO bond energy (67.2 kcal/mol) is weaker than the C−OO bond in a monoperoxide such as CH_3−OOH (68.6 kcal/mol) or CH_3−$OOCH_3$ (69.2 kcal/mol, Table 1).

Effect of Heterocyclic Substitution on Ring Strain Based upon the Cyclization of Acyclic Reference Compounds. Since the dimerization method provides SE relative to a six-membered ring, we need to predict the SE of this set of reference compounds with comparable accuracy. This cyclization method can also address the highly relevant question of whether the introduction of one or more heteroatoms into a ring increases or decreases the strain energy. Although cyclohexane has typically been referred to as strain free, its SE has been calculated by several methods to be about 2.6 kcal/mol.[22a] This modest SE relative to an all-anti paraffin has generally been attributed to the four gauche C−C−C−C interactions present in cyclohexane.[22d] The recent scheme suggested by Lim,[22a] where the strain energy of a specific ring compound is relative to another structurally related *cyclic* reference molecule, provides reliable SE computationally by comparing directly the ab initio energies of the two compounds adjusted to include the energy of the fragment by which they differ.

Monocyclic hydrocarbons differ only by a methylene fragment $(-CH_2-)_n$ where the energy of this strain free fragment, E_{CH_2}, can be derived from all-anti paraffins. The G2 energy differences between all-anti *n*-hexane and *n*-pentane, between *n*-pentane and *n*-butane, as well as between *n*-butane and propane are essentially identical,

(23) (a) For an earlier study at the ab initio (STO-3G) level that suggested a chair (C_{2h}) minimum, see: Stradella, O. G.; Villar, H. C.; Castro, E. A. *THEOCHEM* **1986**, *135*, 1357. (b) We find a twist-chair minimum at both HF and B3LYP/6-31G* levels.

(24) (a) Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* **2002**, *67*, 2588. (b) Bach, R. D.; Ayala, P. Y.; Schlegel, H. B. *J. Am. Chem. Soc.* **1996**, *118*, 12758.

Table 5. Summary of the Calculated Strain Energies (SE) Using Six Different Protocols (A−F)[a]

	A	B	C	D	E	F
 **5**	2.2		2.7	-	1.1[b]	2.2
 **24**	5.6		5.4	6.2	4. 7	5.8
 **25**	26.7		26.1	27.3	25.8	26.7
 **1**	19.1	17.3[c], 19.6[d]	19.8	16.3	15.0	

[a] Protocol A is based upon group equivalent homodesmotic reactions (Table 1). Scheme B is a dimerization (diagonal) protocol (Table 4). Method C is based upon the energy of hydrogenation of the O−O bond (Figure 1). Method D is based upon the energy of hydrogenation of the C−O bond (Figure S1 in the Supporting Information). In Scheme E, the SE is relative to linear reference compound $CH_3CH_2OOCH_2CH_3$ and is based upon successive extrusion of a $-CH_2-$ fragment from the corresponding cyclic peroxide (Figure 2). Method F calculates the SE relative to the corresponding cyclic ether upon peroxide oxygen atom insertion. [b] SE calculated by cyclization of $CH_3CH_2OOCH_2CH_3$ to 1,2-dioxane with the proper correction factors (Table 6). [c] Based upon combination with cyclopropane to form 1,2-dioxane. [d] Based upon the dimerization (diagonal) of DO (see ref 19 for the definition of the diagonal method).

suggesting a leveling effect as the chain length is extended. Thus, the $-CH_2-$ energy correction term (39.22547 au) is relatively constant for hydrocarbons and is not influenced by the paraffin chain length. The energy correction term for each $-CH_2-$ in cyclohexane may be derived by dividing the total energy (G2) of cyclohexane by 6 (39.22484 au). Relative to the above energy correction term from acyclic hydrocarbons, cyclohexane has an SE = 2.4 kcal/mol. 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 provides a very practical method to estimate the strain energy

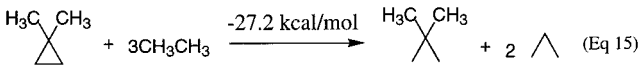
$$\mathrm{SE} = E_{\mathrm{cyclic}} - E_{\mathrm{acyclic}} + E_{\mathrm{corr}}$$

where

$$E_{\mathrm{corr}} = 2E_{\mathrm{C-H}} - E_{\mathrm{C-C}} + 2E_{\mathrm{H}} = 2(E_{\mathrm{CH_3CH_2CH_3}} - E_{\mathrm{CH_3CH_2CH_2}}) - (E_{n-\mathrm{hexane}} - 2E_{\mathrm{CH_3CH_2CH_2}}) + 1.0 = -1.17956 \text{ au}$$

is the energy adjustment for the removal of two hydrogen atoms and formation of the C−C bond attending cyclization. At the G2 level, the calculated SE is 2.2 kcal/mol for cyclohexane relative to all-anti *n*-hexane (Figure 2). *n*-Hexane with two gauche interactions is a minimum that is only 1.3 kcal/mol (G2(MP2)) higher in energy than the all-anti reference compound.

At the G2 level, the SE of cyclopentane (8.0 kcal/mol) cyclobutane (26.9 kcal/mol) and cyclopropane (28.2 kcal/mol) relative to their *acyclic* counterparts may be obtained by the cyclization of the corresponding all-anti acyclic hydrocarbons with the same number of heavy atoms. The SE of 1,1-dimethylcyclopropane by this cyclization reaction with *branched reference compound* 2,2-dimethylpropane (neopentane) is predicted to be 28.0 kcal/mol in excellent agreement with homodesmotic[2] reaction 15.



(Eq 15)

Since electronegative α- and *β*-heteroatom substitution will significantly affect the energy corrections for ring closure to the corresponding cyclic reference compound, we have calculated the influence of such electronegative fragments on the bond dissociation energies (BDE) relevant to the cyclization process. The impact of α-oxygen substitution on the BDE (0.15331 au) and that for a *β*-oxygen (0.16326 au) is presented in Table 6. The BDE for a C−H bond *β* to a peroxo group is indistinguishable from that *β* to an ether functionality. The energy correction factors for C−C bond dissociation/formation (0.13833 au) and for *β*-oxygen substitution (0.14370 au) at the G2-(MP2) level of theory are also described in Table 6.

With energy corrections, using the all-*anti* conformation of ethyl propyl ether as the acyclic reference compound and a *β*-oxo C−C, one *β*-oxo and one *γ*-oxo C−H correction term, an SE = 1.7 kcal/mol is estimated for tetrahydropyran **15** [SE = 1.2 kcal/mol by group equivalent reactions (eq 1)]. The SE of tetrahydrofuran **26** (THF) of 5.0 kcal/mol is based upon the cyclization of diethyl ether and is also in quite good agreement with the SE for THF (5.7 kcal/mol) based upon group equivalent reactions (eq 1) or the $-CH_2$-extrusion method (6.1 kcal/mol).

Using diethyl peroxide (**23**) as the acyclic reference compound with the same number of heavy (non-hydrogen) atoms and the *β*-oxo C−C and C−H correction terms and related BDE, the estimated SE is 1.1 kcal/mol for 1,2-dioxane **5** (1,2-dioxacyclohexane). Thus, it appears that heteroatom substitution and a decrease in gauche interactions outweigh the electron−electron repulsion typically associated with the peroxo moiety. While the experimental $\Delta H_{f(298)}$ of 1,3-dioxane **6** (−80.88 kcal/mol)[18a] is 5.5 kcal/mol lower than that of its 1,4-isomer **14**, the calculated energy of 1,2-dioxane (**5**) is 44.3 kcal/mol higher in energy than 1,4-dioxane. This is not at all surprising since in addition to the weak O−O bond (40.2 kcal/mol for diethyl peroxide) in 1,2-dioxane, the C−O BDE for an ether is 16 kcal/mol greater than the C−O bond in a dialkyl peroxide (Table 1). The greater stability of an alkoxy radical versus an alkyl peroxo radical is also reflected in the weaker O−H BDE for an alkyl hydroperoxide versus an alcohol (ΔBDE = 19.3 kcal/mol). Despite the relatively high internal energy of such cyclic peroxides as 1,2-dioxane, they are not effective oxygen

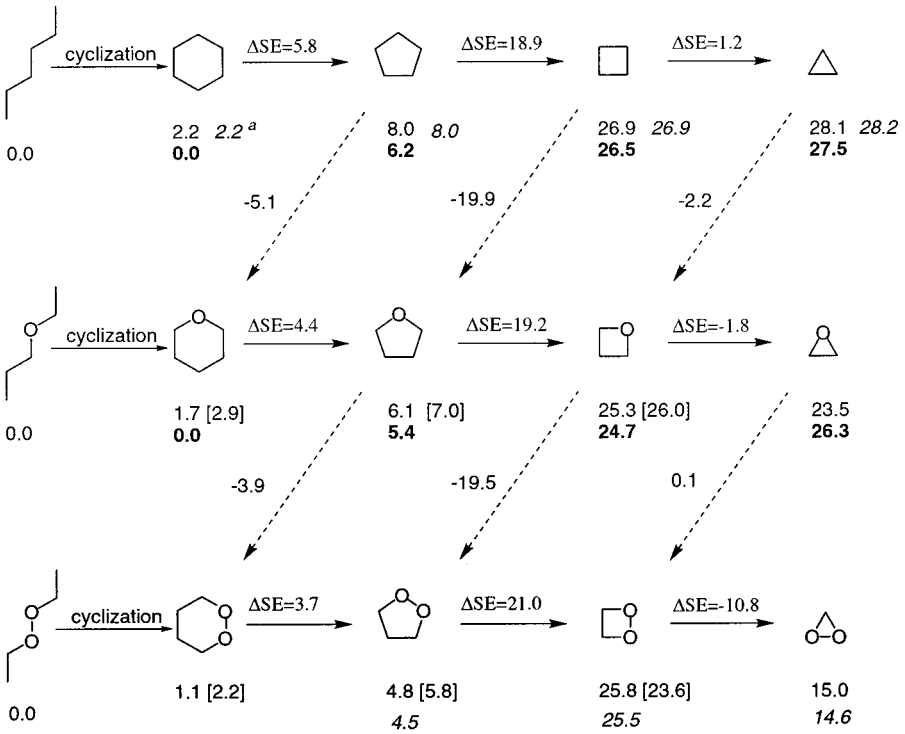


Figure 2. Strain energies [G2(MP2),kcal/mol] based upon the insertion/extrusion of $-CH_2-$/$-O-$ energy equivalents. Relative energies (kcal/mol) of the six-membered ring compounds are based upon the cyclization of acyclic all-anti reference molecules. The ΔSE on the horizontal path are derived from succesive $-CH_2-$ extrusion from larger to smaller cyclic molecules. The SE values in brackes are estimated from the difference in the SE on the horizontal line and the energy of reaction for oxygen insertion given on the dashed diagonal line [resulting from either an ether or a peroxo oxygen insertion into a cyclic hydrocarbon (dashed diagonal arrows) with the requisite number of $-CH_2-$ groups]. The SE in bold type are experimental values taken from ref 19. For these calculations, the following energy corrections have been used. **Hydrocarbons:** $E_{CH2(RR)} = 39.22467$ au. **Ethers:** $E_{\alpha\text{-}CH2(ROR)} = 39.22927$ au, $E_{\beta\text{-}CH2(ROR)} = 39.22425$ au, $E_{-O-} = 75.12344$ au. **Peroxides:** $E_{\alpha\text{-}CH2(ROOR)} = 39.22917$ au, $E_{\beta\text{-}CH2(ROOR)} = 39.22411$ au, $E_{\alpha\text{-}O-} = 75.04998$ au. For a more complete description, see Table 6. Key: (a) The numbers in italics are at the G2 level of theory.

Table 6. Bond Energies (au) for Ring Closure of Acyclic to Cyclic Reference Compounds (Numbers in Parentheses Are in kcal/mol)

correction formula	G2(MP2) au (kcal/mol)	G2 au (kcal/mol)
hydrocarbons		
$E_{C-H} = E_{CH_3CH_3} - (E_{CH_3CH_2} + E_H)$	0.16081 (100.91)	0.16056 (100.75)
$E_{C-H} = E_{CH_3CH_2CH_3} - (E_{CH_3CH_2CH_2} + E_H)$	0.16183 (101.55)	0.16177 (101.51)
$E_{C-C} = E_{CH_3CH_3} - 2E_{CH_3}$	0.14111 (88.55)	0.14072 (88.30)
$E_{C-C} = E_{butane} - 2E_{CH_3CH_2}$	0.14140 (88.73)	0.14046 (88.39)
$E_{C-C} = E_{hexane} - 2E_{CH_3CH_2CH_2}$	0.14440 (90.61)	0.14398 (90.35)
ethers		
$E_{\alpha\text{-}CH(ROR)} = E_{CH_3CH_2OCH_3} - (E_{CH_3CH_2OCH_2} + E_H)$	0.15336 (96.23)	0.15331 (96.20)
$E_{\beta\text{-}CH(ROR)} = E_{CH_3CH_2OCH_2CH_3} - (E_{CH_3CH_2OCH_2CH_2} + E_H)$	0.16336 (102.51)	0.16326 (102.45)
$E_{\gamma\text{-}CH(ROR)} = E_{CH_3CH_2OCH_2CH_2CH_3} - (E_{CH_3CH_2OCH_2CH_2CH_2} + E_H)$	0.16151 (101.35)	
$E_{\alpha\text{-}C-C(ROR)} = E_{CH_3CH_2OCH_2CH_3} - (E_{CH_3CH_2OCH_2} + E_{CH_3})$	0.13872 (87.05)	0.13833 (86.80)
$E_{\beta\text{-}C-C(ROR)} = E_{CH_3CH_2OCH_2CH_2CH_3} - (E_{CH_3CH_2OCH_2CH_2} + E_{CH_3})$	0.14370 (90.17)	
$E_{C-O(ROR)} = E_{CH_3CH_2OCH_2CH_3} - (E_{CH_3CH_2O} + E_{CH_3CH_2})$	0.14056 (88.20)	0.13920 (87.24)
peroxides		
$E_{\alpha\text{-}CH(ROOR)} = E_{CH_3OOCH_2CH_3} - (E_{CH_3CH_2OOCH_2} + E_H)$	0.08894 (55.81)	0.08816 (55.32)
$E_{\beta\text{-}CH(ROOR)} = E_{CH_3OOCH_2CH_3} - (E_{CH_3OOCH_2CH_2} + E_H)$	0.16366 (102.70)	0.16355 (102.63)
$E_{\alpha\text{-}C-C(ROOR)} = E_{CH_3CH_2OOCH_2CH_3} - (E_{CH_3CH_2OOCH_2} + E_{CH_3})$	0.07425 (46.59)	0.07315 (45.90)
$E_{C-O(ROOR)} = E_{CH_3CH_2OOCH_2CH_3} - (E_{CH_3CH_2OO} + E_{CH_3CH_2})$	0.11285 (70.81)	0.11159 (70.02)
$E_{O-H(ROOH)} = E_{CH_3CH_2OOH} - (E_{CH_3CH_2OO} + E_H)$	0.1359 (85.28)	0.13524 (84.86)
$E_{O-O(ROOR)} = E_{CH_3CH_2OOCH_2CH_3} - 2E_{CH_3CH_2O}$	0.06592 (41.37)	0.06402 (40.17)
alcohols		
$E_{C-O(ROH)} = E_{CH_3CH_2OH} - (E_{CH_3CH_2} + E_{OH})$		0.15021 (94.26)
$E_{O-H(ROH)} = E_{CH_3CH_2OH} - (E_{CH_3CH_2O} + E_H)$		0.16687 (104.71)
amines		
$E_{\alpha\text{-}CH(RNHR)} = E_{CH_3CH_2NHCH_3} - (E_{CH_3CH_2NHCH_2} + E_H)$	0.14787 (92.79)	0.14779 (92.74)
$E_{\beta\text{-}CH(RNHR)} = E_{CH_3CH_2NHCH_2CH_3} - (E_{CH_3CH_2NHCH_2CH_2} + E_H)$	0.16198 (101.64)	0.16190 (101.59)
$E_{\alpha\text{-}C-C(RNHR)} = E_{CH_3CH_2NHCH_2CH_3} - (E_{CH_3CH_2NHCH_2} + E_{CH_3})$	0.13126 (82.37)	0.13084 (82.10)
$E_{\beta\text{-}C-C(RNHR)} = E_{CH_3CH_2NHCH_2CH_2CH_3} - (E_{CH_3CH_2NHCH_2CH_2} + E_{CH_3})$	0.14250 (89.42)	

atom donors because in most cases a low activation pathway does not exist for oxygen atom transfer.

The energetics of cyclization of the acyclic reference molecules (see also Figure 2) provides six-membered ring reference compounds that have SE of 1−2 kcal/mol. The very low predicted SE of 1,2-dioxacyclohexane (**5**) is essential to the validity of the dimerization method (Table 4) that is dependent upon **5** as the relatively strain free

Table 7. Energy Correction (au) for Expansion/Extrusion by Methylene (−CH_2−) and Oxygen (−O−) Insertion

correction formula	G2(MP2)	G2
hydrocarbons		
$E_{CH_2(RR)} = E_{CH_3CH_2CH_2CH_2CH_2CH_3} - E_{CH_3CH_2CH_2CH_2CH_3}$	39.22467	39.22547
ethers		
$E_{\alpha\text{-}CH_2(ROR)} = E_{CH_3CH_2OCH_2CH_3} - E_{CH_3CH_2OCH_3}$	39.22927	39.23011
$E_{\beta\text{-}CH_2(ROR)} = E_{CH_3CH_2OCH_2CH_2CH_3} - E_{CH_3CH_2OCH_2CH_3}$	39.22425	
$E_{\alpha\text{-}O(ROR)} = E_{CH_3CH_2OCH_2CH_2CH_3} - E_{CH_3CH_2CH_2CH_2CH_3}$	75.12344	
amines		
$E_{\alpha\text{-}CH_2(RNHR)} = E_{CH_3CH_2NHCH_2CH_3} - E_{CH_3CH_2NHCH_3}$	39.22730	39.22814
$E_{\beta\text{-}CH_2(RNHR)} = E_{CH_3CH_2NHCH_2CH_2CH_3} - E_{CH_3CH_2NHCH_2CH_3}$	39.22443	
$E_{\alpha\text{-}NH(RNHR)} = E_{CH_3CH_2NHCH_2CH_2CH_3} - E_{CH_3CH_2CH_2CH_2CH_3}$	55.25637	
peroxides		
$E_{\alpha\text{-}CH_2(ROOR)} = E_{CH_3CH_2OOCH_3} - E_{CH_3OOCH_3}$	39.22917	39.23002
$E_{\beta\text{-}CH_2(ROOR)} = E_{CH_3CH_2CH_2OOCH_3} - E_{CH_3CH_2OOCH_3}$	39.22411	39.22489
$E_{\alpha\text{-}O(ROOR)} = E_{CH_3CH_2CH_2OOCH_3} - E_{CH_3CH_2OCH_2CH_3}$	75.04998	75.05225
$E_{\alpha\text{-}O(ROOR)} = E_{CH_3OOCH_3} - E_{CH_3OCH_3}$	75.05018	75.05242

reference compound for the series of cyclic peroxides. In general, heteroatoms tend to slightly *reduce* the SE of cyclic molecules.

Comparative SE Based upon the Energetics of the Insertion of −CH_2−, −O−, and −NH− Equivalents into Cyclic Molecules. We have developed a method for predicting the SE of small ring compounds that does not depend on the ability to balance exactly homodesmotic equations. For example, the formal insertion or extrusion of a −CH_2− fragment in a cyclic hydrocarbon molecule and deriving the SE from differences in the total energies provides calculated SE in excellent agreement with experiment (Figure 3). This is especially true when only closed shell species are involved and the energy equivalents are obtained at the G2 level (Table 7). The SE of the series of hydrocarbons varies in the expected manner as the ring size decreases.

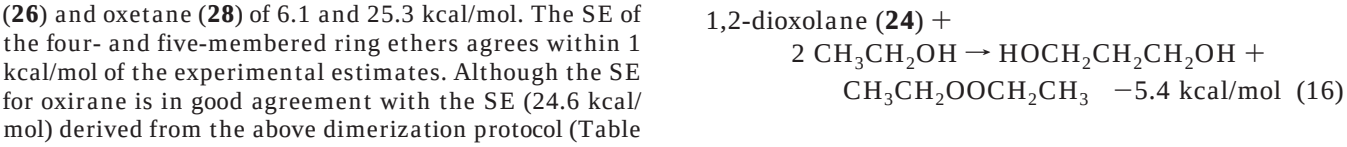
The strain energies of cyclic ethers may also be predicted quite accurately by incremental ring expansion/contraction with methylene energy equivalents.

The SE of oxirane **13**, 26.6 kcal/mol, is based upon the sequential expansion/contraction motif, starting with ethyl propyl ether (**27**) as the acyclic reference compound (Figure 2). Cyclization of **27** to tetrahydrohydropyran (**15**) suggests an SE for the six-membered ring reference of only 1.7 kcal/mol. Successive extrusion of a −CH_2− fragment from **15** suggests an SE for tetrahydrofuran (**26**) and oxetane (**28**) of 6.1 and 25.3 kcal/mol. The SE of the four- and five-membered ring ethers agrees within 1 kcal/mol of the experimental estimates. Although the SE for oxirane is in good agreement with the SE (24.6 kcal/mol) derived from the above dimerization protocol (Table 4) both oxirane and DO are predicted to be several kcal/mol lower by this method possibly implicating the accuracy for the α-CH_2 correction term of three-membered rings (Table 7).

Of particular interest to the present study, this method provides an additional check on the SE of cyclic peroxides. The cyclization of diethyl peroxide suggests an SE for 1,2-dioxane of 1.1 kcal/mol. Consistent with the above results, the SE of 1,2-dioxetane is 21 kcal/mol greater than that of 1,2-dioxolane but is also 10.8 kcal/mol greater than that of DO! Thus, we provide additional corroborative evidence for the relatively low SE for the parent dioxirane **1** (14.6 kcal/mol), a value consistent with the trends noted for the dimerization method (16.9 and 19.6 kcal/mol, G2(MP2)) and homodesmotic reactions 3−6 (19 kcal/mol). Of course, both dimerization methods provide SEs relative to a cyclic reference compound and consequently the numbers quoted should be reduced by 2 kcal/mol.

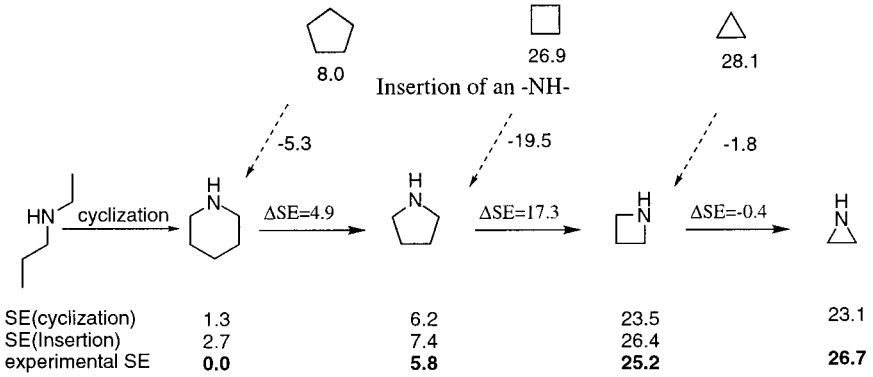
A fundamental enigma is the fact that dioxiranes are considerably less strained than their four-membered ring peroxo-analogues. The SE of three-membered ring hydrocarbons, ethers, and amines are all slightly greater than the other four-membered ring compounds.[22] The relatively small difference in the SE of cyclopropane and cyclobutane may be attributed to the fact that the BDE of the C−H bonds in cyclopropane are significantly greater (110.3 kcal/mol) that those of cyclobutane (101.9 kcal/mol).[24a] The greater C−C−C angular strain in the former is offset by its much stronger C−H bonds. The clear exception to this trend is the cyclic peroxides where dioxirane is less strained than dioxetane by 8−11 kcal/mol. It is also obvious that 1,2-dioxetanes have SEs comparable to the other four-membered ring compounds considered (25−27 kcal/mol). Thus, *it is the dioxiranes that have lower strain energies and in particular DMDO is even less strained than DO by 7 kcal/mol due to the gem-dimethyl stabilization effect.*

The SE of 1,2-dioxolane **24**, as predicted from formal reaction 16, is also in good agreement with the strain energy based upon the −CH_2− extrusion reaction (4.8 kcal/mol, Figure 2). The group equivalent protocol[4] of eq 1 provides excellent estimates of the SE of cyclic peroxides with ring sizes greater than three i.e., the reference diols do not have a 1,3-dioxa arrangement.



This method for correlating the relative SE among different classes of compounds also supports the relatively low SE of 1,2-dioxolane **24** where insertion of an −O− into oxetane **28** suggests that **24** is 19.5 kcal/mol less strained. Since the experimental SE of cyclic ether **28** is 24.7 kcal/mol, the SE of 1,2-dioxolane **24** must be on the order of 5 kcal/mol. This estimated SE for **24** places the SE of its isomer DMDO, relative to an unbranched reference compound, at 1−2 kcal/mol. The SE of DMDO relative to reference compound 1,3-propanediol is only 1.3 kcal/mol.[24a] As noted below, the total energy of DMDO is 3.4 kcal/mol *lower* than that of 1,2-dioxolane in excellent support of their estimated relative stabilities. However, we should not lose sight of the fact that although 1,2-dioxolane has a relatively low SE, it is still a high energy peroxide with a weak O−O bond (<40 kcal/mol).[24b] Isomerization to 1,3-dioxolane is attended by the liberation of 48.0 kcal/mol reflecting the formation

Scheme 1



of two much stronger C−O bonds. The strain energy in a molecule is derived by convention and hence cyclopentane, a molecule of much greater thermodynamic stability than 1,2-dioxolane, actually has a slightly *higher* SE.

The thermodynamic stability of DMDO is largely a consequence of the combined dioxa and dimethyl-geminal effects and its associated strong C−H bonds relative to those in dioxolane.[25] A qualitative estimate of this effect comes from a comparison of the C−H bond dissociation energies (BDE) in DMDO versus those in 1,2-dioxacyclopentane (dioxolane); the sum of the C−H bond BDE in DMDO is 24.7 kcal/mol (ΔH^{298}, G2(MP2))[25] lower in energy. The C−CH_3 BDE in DMDO is also atypically strong at 98.9 kcal/mol. A strong stabilizing interaction between the peroxo bond in DMDO and its C−CH_3 bonds is evidenced by the fact that the C−CH_3 BDE in reference molecule 2,2-dihydroxycyclopropane is reduced to 92.9 kcal/mol. Thus, in the absence of ring strain DMDO should in principle be much more stable (as is 2,2-dihydroxypropane more stable than its 1,3-isomer) but it is the strain energy in DMDO (SE ≈ 11 kcal/mol) that *raises its total energy* to within 3.4 kcal/mol of that of 1,2-dioxolane **24**.

It is also important to understand, from a pedagogical perspective, the interrelationship between strain energies of different classes of molecules of the same ring size. For example, by this method we can compare the relative strain energies of cyclic hydrocarbons with their mono- and dioxygen cyclic counterparts. The insertion of an ether oxygen equivalent (75.12344 au; derived form the energy difference between acyclic ethyl propyl ether and *n*-pentane, Table 7) into cyclopropane provides a comparison of its SE with that of four-membered cyclic ether oxetane **28**. This exercise gives a relative SE for these two compounds that differ by 2.2 kcal/mol (diagonal element, Figure 2) in agreement with the SE (25.9 kcal/mol) calculated by the contraction of THF (25.3 kcal/mol) by one −CH_2− energy fragment. It is of interest to note that, by this method, oxirane is less strained (1.8 kcal/mol) than oxetane.

Similar insertion of an α-peroxo −O− equivalent (75.04998 a.u.; Table 7) into oxirane (ΔE = 0.1 kcal/mol) suggests that the SE of oxirane (**13**) and the four-membered ring peroxide 1,2-dioxetane (**28**) are essentially identical. The SE of 1,2-dioxetane based upon homodesmotic reaction 17 is predicted to be 26.0 kcal/mol (G2) in excellent agreement with the SE predicted on the basis of extrusion data (Figure 3).

1,2-dioxetane (**13**) + 2 CH_3OCH_3 → $CH_3OCH_2CH_2OCH_3$ + CH_3OOCH_3 −26.0 kcal/mol (17)

In a similar fashion, ring closure of ethyl propylamine to piperidine **17** with the energy correction for nitrogen (E_{corr} = −1.18146 au, G2(MP2)) suggests an SE of 1.3 kcal/mol. The SE of pyrrolidine **29** based upon the cyclization of diethylamine is predicted to be 6.2 kcal/mol, a value that is close to the 6.0 kcal/mol based upon the group equivalent method (Table 1). Insertion of an −NH− energy equivalent into cyclopropane suggests that the SE (26.4 kcal/mol) of the corresponding four-membered ring amine is 1.8 kcal/mol less than that of cyclopropane and about a 1 kcal/mol higher than the experimental estimate of 25.2 kcal/mol. This insertion method suggests that the SE of pyrrolidine is 19.5 kcal/mol less than that of cyclobutane and that the SE of piperidine is 5.3 kcal/mol less than that estimated for cyclopentane (Scheme 1).

Conclusions

1. The dimerization (diagonal)[19] method provides the simplest form of a balanced reaction that provides reliable strain energies for a broad class of hydrocarbons, heterocycles and peroxides based upon the dimerization of a three-membered ring molecule or its combination with cyclopropane to form a six-membered ring reference compound.

2. Group equivalent reactions,[4] which conserve the next nearest neighbor bonding concept maintaining the same molecular environment on both sides of the equation, provide a highly reliable method for determining the strain energies of three- to six-membered ring compounds. The method provides accurate SEs for cyclic peroxides with ring sizes greater than three.

3. The cyclization protocol based upon the energy terms balancing the difference between the cyclic and acyclic reference compound provides highly reliable SE for four to six-membered rings.

4. The simple process of insertion/extrusion of −CH_2−, −O−, and −NH− fragments to allow the reversible interconversion of hydrocarbons to ethers, secondary amines and peroxides provides a unique method to interrelate the SE of different classes of compounds of varying ring size. All of the above methods concur with the reduced assessment of the inherent strain of diox-

(25) (a) The BDE for the C−H bond of DMDO are 101.2 kcal/mol and the α and β C−H BDE in dioxolane are 95.1 and 100.9 kcal/mol (G2(MP2)).

iranes and place the strain energy of these three-membered ring peroxides much lower than cyclopropanes, epoxides, aziridines, and 1,2-dioxetanes.

6. The relative SE of DMDO is predicted to be about 7 kcal/mol less than that of DO as a result of the geminal dimethyl substitution effect. The SE of DMDO is ≈11 kcal/mol with respect to a *gem*-dimethyl reference molecule. The calculated total energy (G2) of DMDO is 3.4 kcal/mol (−2.6 at CBS-APNO) lower in energy than its isomeric five-membered ring peroxide, 1,2-dioxacyclopentane. *gem*-Difluoro substitution destabilizes a cyclopropane ring by about 14 kcal/mol and has a 7 kcal/mol destabilizing effect upon the relative stability of a dioxirane.

7. The relatively low SE for DMDO is a striking observation that greatly impacts how we now think about the origin of its reactivity since we have traditionally regarded it as a "highly strained cyclic peroxide" that can oxidize saturated hydrocarbons. Quite obviously, the reactivity of this versatile oxidant must be ascribed to reasons other than its strain energy. If DMDO does involve singlet biradicloid character along the reaction pathway for abstraction of a hydrogen atom in a concerted C−H insertion reaction,[24a] then the effective relief of ring strain should be measured relative to its gem-dimethyl reference compound and be on the order of 10−11 kcal/mol. However, in a two-electron oxidation such as alkene epoxidation where the pathway effectively involves the transfer of an oxygen atom with the S_N2-like displacement of an acetone molecule, then the relief of strain may be lessened and provide a rationale for why the theoretically derived activation barriers for the epoxidation of alkenes by the unstrained peroxy acids and DMDO are quite similar.[26] As reported by Cremer,[9b] the parent dioxirane decomposes at 298 K with an activation enthalpy of 18 kcal/mol to bis-oxomethylene diradical while the barrier to ring opening of DMDO is 23 kcal/mol which accounts for its short but sufficient half-life and its capacity to serve as a useful chemical oxidant.

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Supporting Information Available: Table S1 [total electronic energies calculated at the G2, G2(MP2), CBS-Q, and B3LYP/6-311+G(3df,2p) levels of theory]. Table 2S [CBS-APNO energies of the selected compounds and corresponding QCISD/6-311G(d,p) geometries]. Figure S1 (energies of hydrogenation of cyclic peroxides and strain energies relative to the acyclic reference compound, diethyl peroxide, at the G2 level of theory). Appendix (Cartesian coordinates of the compounds from Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

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