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The Effect of Substitutents on the Strain Energies of Small Ring Compounds

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The effect of substitutents on the strain energy (SE) of cyclic molecules is examined at the CBS, G2, and G2(MP2) levels of theory. Alkyl substitutents have a meaningful effect upon the SE of small ring compounds. *gem*-Dimethyl substitution lowers the strain energy of cyclopropanes, cyclobutanes, epoxides, and dimethyldioxirane (DMDO) by 6−10 kcal/mol relative to an unbranched acyclic reference molecule. The choice of the reference compound is especially important for geminal electronegative substitutents. The SE of 1,1-difluorocyclopropane is estimated to be 20.5 kcal/mol relative to acyclic reference molecule 1,3-difluoropropane but is 40.7 kcal/mol with respect to the thermodynamically more stable ($\Delta E = -20.2$ kcal/mol) isomeric reference compound 2,2-difluoropropane. The SE of dioxirane (DO) is estimated to be ≈18 kcal/mol while the SE of DMDO is predicted to be ≈11 kcal/mol by using homodesmotic reactions that maintain a balanced group equivalency. The total energy (CBS-APNO) of DMDO is 2.6 kcal/mol lower than that of isomeric 1,2-dioxacyclopentane that has an estimated SE of 5 kcal/mol. The thermodynamic stability of DMDO is a consequence of its relatively strong C−H (BDE = 102.7 kcal/mol) and C−CH_3 (BDE = 98.9 kcal/mol) bonds. By comparison, the calculated *sec*-C−H and -C−CH_3 G2 bond dissociation energies in propane are 100.3 and 90.5 kcal/mol.

Introduction

The use of ring strain concepts in explanation of reactivity trends has played an important role in mechanistic organic chemistry.[1] Over the years it has been particularly useful for the practicing organic chemist, as a point of calibration, to remain cognizant of the relative strain energy (SE) of the simplest series of unsubstituted cyclic hydrocarbons[7] such as cyclohexane (SE = 0.0 kcal/mol), cyclopentane (6.2 kcal/mol), cyclobutane (26.5 kcal/mol), and cyclopropane (27.5 kcal/mol). The relief of ring strain energy, SE, is often invoked to explain the enhanced reactivity of transformations involving small ring compounds where relief of strain occurs on the reaction coordinate even though it is recognized that ring strain energy is a relative quantity. The excess energy inherent in a cyclic molecule relative to an appropriately selected strain-free molecule may be obtained as an experimental quantity from heats of formation (ΔH_f) using enthalpic strain-free quantities for specific molecular fragments (e.g., CH_3, CH_2, CH, O−O, etc.) referred to as group equivalents.[2] Actual strain energies are somewhat subjective since the difference between the measured heat of formation for the cyclic compound and a hypothetical strain-free ΔH_f, derived from chemical groupings, is what is commonly referred to as the ring strain energy. The strain energy can be defined also as the reaction energy of a balanced chemical transformation where the reactants and products differ by the presence of a ring. Isodesmic,[3] homodesmotic,[4] and group equivalent schemes[5] have been proposed to measure such ring strain energies. Conventional strain energy[6] may be determined from thermochemical group additivity increments, isodesmic bond separation energies (eq 1), and homodesmotic separation energies (eq 2). An isodesmic reaction has the same number and types of bonds in both reactants and products while a homodesmotic chemical reaction attempts to preserve both the bond type and the valence characteristics of each of the participants. In the present work we expand upon the concept of group equivalent reactions that maintain, as closely as possible,

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[3] Hehre, W. J.; Ditchfield, R.; Radom, L.; Pople, J. A. *Am. Chem. Soc.* **1970**, *92*, 4796.

[4] (a) George, P.; Trachman, M.; Bock, C. W. Brett, A. M. *Tetrahedron* **1976**, *32*, 317. (b) Benson, S. W.; Buss, J. H. *J. Chem. Phys.* **1958**, *29*, 546. (c) Dill, J. D.; Greenberg, A.; Liebman, J. F. A. *Am. Chem. Soc.* **1979**, *101*, 6814.

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[6] (a) Cremer, D.; Kraka, E.; Szalay, P. G. *Chem. Phys. Lett.* **1998**, *292*, 97. (b) With a $\Delta H_{f(298)}$ derived from the experimental heat of formation of formic acid (−90.60 kcal/mol) and a calculated$\Delta\Delta H_{(298)} = -90.44$ between formic acid and DO (G2), the $\Delta H_{f(298)}$ for dioxirane (−0.2 kcal/mol) is in excellent agreement with the value suggested by Cremer ($\Delta H_{f(298)} = -0.3$ kcal/mol)[6a] at the CCSD level. The $\Delta H_{f(298)}$ of DO derived from atomization energies at the G2 level is −2.07 kcal/mol. (c) Kraka, E.; Konkoli, Z.; Cremer, D.; Fowler, J.; Schaefer, H. F. *J. Am. Chem. Soc.* **1996**, *118*, 10595. (d) Cremer, D.; Gauss, J.; Kraka, E.; Stanton, J. F.; Bartlett, R. J. *Chem. Phys. Lett.* **1993**, *209*, 547 (e) Cremer, D.; Kraka, E. *J. Am. Chem. Soc.* **1985**, *107*, 3800. (f) Although it has been suggested that f orbitals are required to get accurate O−O bond distances in certain peroxides,[6a] our data (Table 5) suggests that the larger basis set has a modest influence on the relative energies of the isomeric peroxides but does not change the relative stabilities of DMDO and 1,2-dioxolane.

[7] For a recent discussion of the basic concepts involved in estimating strain energies, see: (a) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 4450 (b) Alcami, M.; Mo. O.; Yanez, M. *J. Comput. Chem.* **1998**, *19*, 1072 and references therein.

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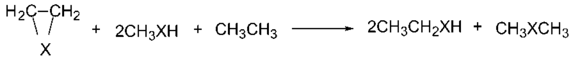
the exact bonding environment (i.e. the same number of C, O, and H atoms bound to each atomic center) on both sides of the equation.[5]


(Eq 1)


(Eq 2)

The recent scheme suggested by Lim,[7a] 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 strain energy of cyclohexane, relative to the strain free reference compound all-*anti*-*n*-hexane, can 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 $SE = E_{cyclic} - E_{acyclic} + E_{corr}$ where $E_{corr} = 2E_{C-H} - E_{C-C} + 2E_H$ is the energy adjustment for the removal of two hydrogen atoms and formation of the C−C bond attending cyclization.[8] At the G2 level this method can provide energetics with near chemical accuracy.

We also utilize a method for predicting the SE of small ring compounds relative to a six-membered ring based upon the dimerization of the three-membered ring participants to a six-membered ring reference compound. The experimental $\Delta H_f = -4.926$ kcal/mol for the normal methylene fragment for a straight-chain hydrocarbon is essentially identical to that of cyclohexane (−4.920 kcal/mol per methylene group).[1b] Because of this close agreement in the heat contents, cyclohexane is generally taken as strain-free. However, a comparison of the experimental $\Delta H^\circ_{f(liq)} = -37.39$ kcal/mol of cyclohexane with the difference in $\Delta H^\circ_{f(liq)}$ for *n*-hexane (−47.48 kcal/mol) versus *n*-pentane (−41.47 kcal/mol) suggests a $\Delta\Delta H^\circ_{f(liq)}$ of 0.22 kcal/mol (per CH_2) or a SE for cyclohexane of 1.3 kcal/mol. At the G2 level, this same exercise comparing ΔH^{298} suggests a $\Delta\Delta H_{298} = 0.26$ kcal/mol or a SE of 1.6 kcal/mol. These estimates are more consistent with the bulk of the other data we have suggesting a SE for cyclohexane ≈2 kcal/mol

We were stimulated initially to reexamine the strain energy of the parent dioxirane **1** (DO) because earlier estimates of its SE (32.8 kcal/mol)[6c] approached the magnitude of a typical bond dissociation energy (BDE) for a generic O−O bond (≈33 kcal/mol).[9] Since the suggested SE of DO was greater than that of cyclopropane, it was proposed that an additional oxygen atom incorporated into the ring of oxirane *increases* the ring strain by 5−6 kcal/mol due to enhanced lone-pair lone-pair electron repulsion. A decrease in ring strain upon fluorination of three-membered rings was also predicted from the ring strain enthalpies of difluorocyclopropane (23.6 kcal/mol) or difluorodioxirane of 20.8 kcal/mol.[6a] The O−O BDE of a generic peroxide has now been increased to ≈45 kcal/mol[9] and a more recent lower estimate of the strain energy of dioxirane (SE = 26.4 kcal/mol)[6a] based upon a revised $\Delta H_{f(298)}$ for DO,[6b] appeared to be more consistent with what one would anticipate for the thermodynamic stability of such versatile oxidants as dimethyldioxirane **2** (DMDO). Our recent predictions[8] for the SE of DO (18 kcal/mol) and DMDO (≈11 kcal/mol) are much lower than anticipated, and in this paper we attempt to provide a rationale for this unusual observation.

Computational Methods

Ab initio molecular orbital calculations[10] were performed with the GAUSSIAN 98 system of programs.[11] For preliminary calculations, 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 the calculations using density functional theory (DFT). Geometries were optimized[14] in some cases, at B3LYP/6-311+G(3df,2p). The B3LYP level of theory has been shown to give adequate geometries for a series of reactions with peracids but the activation barriers for epoxidation are systematically lower by 5−8 kcal/mol relative to the QCISD(T) level.[15] The reaction enthalpies and strain energies were calculated using G2 and in some cases G2(MP2) and CBS theory.[16] Although the G2 method is generally considered to be reliable to about 1.2 kcal/mol, the molecule set of 125 compounds used to calibrate the method did not include ring systems or C−F bonds. 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(d)),[6a] 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. CBS-Q theory provides energetics equal or slightly better than G2 theory while the CBS-APNO method is reliable to about 0.5 kcl/mol. Zero point energies (ZPE) and thermal corrections to obtain reaction enthalpies at 298 K in the G2 series are by convention computed at the HF/6-31G(d) level and those at the B3LYP/6-31G(d) level were scaled by 0.9806 according to Scott and Radom.[17] Experimental heats of formation were taken from NIST.[18] Homolytic bond energies (ΔE) quoted in the text are derived from G2 total energies while bond

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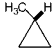
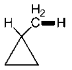
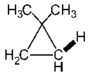
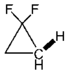
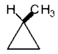
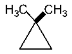
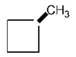
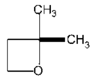
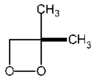
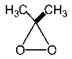
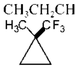
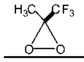
Table 1. Calculated C−H, C−C, and C−F Bond Energies (Δ*E*, kcal/mol) and Bond Dissociation Energies (BDE = ΔH°_{298}, kcal/mol) at the G2(MP2) and G2 Levels of Theory for Selected Characteristic Compounds Used in Homodesmotic Reactions. The Numbers in the Last Column (BDE_{exp}, kcal/mol) Are Experimental

	Bond type	ΔE (G2(MP2))	ΔE (G2)	BDE (G2) ΔH°_{298}	$BDE_{exp.}$
	C—H				
cyclopropane	C—H	108.90	108.82	110.32	106.3[a]
cyclobutane	C—H	103.83	100.20	101.94	
cyclopentane	C—H	96.30	96.21	97.84	
CH_3—H	C—H	104.01	104.04	105.80	
CH_3CH_2—H	CC—H	100.91	100.85	102.61	98.2[a]
$CH_3CH_2\ CH_2$—H	1° C—H	101.54	101.51	103.26	101.0[b]
CH_3(HC—H)CH_3	2° C—H	98.59	98.47	100.28	99.1[b],98.6[c],99.4[d]
$(CH_3)_3CCH_2$—H	CC—H	99.57	102.25	103.95	
$(CH_3)_3C$—H	CC—H	97.08	96.92	98.79	
dioxirane (DO)	C—H	102.28	102.26	103.73	
dimethyldioxirane (DMDO)	C—H	101.01		102.65[c]	
1,2-dioxacyclobutane	C—H	102.42	102.43	103.73	
1,3-dioxacyclobutane	α-C—H	94.47	94.46	95.86	
1,2-dioxacyclopentane	α-C—H	95.61		96.62[e]	
1,2-dioxacyclopentane	β-C—H	100.76		102.35[c]	
CH_3CH_2OH	α-C—H			94.9[f]	
CH_3CH_2OH	β-C—H			101.9[f]	
	CC—H	106.11	106.02		
	C—H	98.05	98.00		
	CC—H	109.00	108.94		
	CC—H	110.29	110.19	111.69	
$CH_3CF_2CH_2$—H	FCC—H	104.80		106.55[e]	
FCH_2CH_2(CH—H) F	FCC—H(F)	98.66		100.14[e]	
FCH_2 (CH—H) CH_2F	FCC—H	101.55		103.24[e]	
FCH_2CH_2—H	FCC—H	103.08	102.99	104.73	
CH_3CF_2—H	F2C—H	101.01	100.92	102.46	
	C—C				
CH_3—CH_3	C—C	88.55	88.30	90.81	90.4[a]
CH_3CH_2—CH_3	C—CC	88.51	88.19	90.46	85.8[a], 88.2[b], 86.2[d]
CH_3CH_2—CH_2CH_3	CC—CC	88.73	88.39		
$(CH_3)_3C$—CH_3	C—CC	88.17	87.75	90.02	
$CH_3CH_2CH_2$—$CH_2CH_2CH_3$	CC—CC	90.61	90.35		
	C—CC	98.71	98.46		
	C—CC	97.42	97.10		
	C—CC	94.65	90.81	92.86	
	C—CO	88.07	87.79	89.65	
	C—CO	89.47		91.23[e]	
	C—CO	97.33	97.08	98.93	
CH_3CF_2—CH_3	F_2C—C	96.47	96.20		
FCH_2CH_2—CH_3	FC C—C	90.61	90.25	92.37	
FCH_2CH_2—CH_2F	FC C—CF	92.42	92.09		
$CH_3CF_2CH_2$—CH_3	FC C—CC	92.28			
CH_3CF_2—CH_2CH_3	F_2C—C	96.71			
CH_3CH_2—CF_3	C—C F_3	103.59			
$(CH_3)_3C$—CF_3	C—C F_3	104.09			
$CH_3CH_2CH_2CH_2$—CF_3	C—C F_3	104.80			
	C—C F_3	112.26			
	OC—C F_3	101.10			
	C—F				
CH_3—F	C—F	108.89	110.64	112.36	
CH_3CH_2—F	C—F	112.45	114.17	115.70	
$CH_3CH_2\ CH_2$—F	C—F	113.02	114.75		
CH_2(CF—F)CH_3	C—F	122.51	124.37		
	C—F	123.39	126.11		

[a] 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. [b] Based upon experimental heats of formation of methyl radical, ethyl radical, and propane (NIST, ref 18). [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**, *193*, 5930. [e] The values for BDE (ΔH°_{298}) are calculated at the G2(MP2) level of theory. [f] The BDEs are taken from Curtiss, L. A.; Lucas, D. J.; Pople, J. A. *J. Chem. Phys.* **1995**, *102*, 3292.

dissociation energies (BDE) are derived from ΔH_{298}. Throughout the text, bond lengths are in angstroms and bond angles are in degrees. All energy values quoted in the text are at the G2 level unless specified otherwise.

Results and Discussion

1. The Effect of Substitutents on the Strain Energies of Cyclopropanes and Cyclobutanes. The significant differences in the predicted SE for dioxiranes based upon our recent studies[8] suggest that we systematically examine the effects of substitution on the strain energies of small ring compounds in general. A thorough understanding of the energetic consequences of methyl, oxygen, fluorine, and trifluoromethyl substitution on a cyclopropane ring itself seemed a prudent place to start before we attempt to understand how substitutents effect the SE of the more "electronically challenged" dioxiranes.

(a) Methyl Substitutents. Although tradition dictates that an unbranched or all-*anti*-straight-chain hydrocarbon be used as a reference compound for the estimation of strain energies of simple unsubstituted cyclic molecules, the increased thermodynamic stability of branched hydrocarbons makes the choice of the acyclic reference compound problematic. To date, there has not been a systematic study of the effects of substitutents on the SE of even simple hydrocarbons. For example, the stabilizing effect of *gem*-dimethyl substitution is expressed by the isomerization of *n*-butane to isobutane (−2.0 kcal/mol) and *n*-pentane to neopentane (−5.2 kcal/mol, G2) (Table S1). The lower energy of the branched hydrocarbon is thought to be due to the greater number of stronger methyl group C−H bonds (compare C−H BDEs in Table 1, 104.0 kcal/mol for neopentane and 97.8 kcal/mol for cyclopentane). An imbalance in the number and type of C−H bonds can introduce an error in homodesmotic equations since the G2 bond dissociation energy of a C−H bond in ethane is 102.6 kcal/mol (Table 1) while the C−H BDE of the primary and *sec*-C−H bonds in propane are 103.3 and 100.3 kcal/mol.[19a] The effect of C−H BDE can be particularly important for cyclopropanes where Borden[19b] has demonstrated that the major source of strain that results from the introduction of each trigonal (sp^2) carbon center into a cyclopropane is not an increase in angle strain but the loss of a very strong cyclopropane C−H bond. Thus, the long-standing con-

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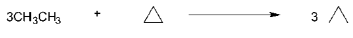
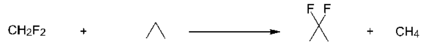
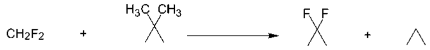
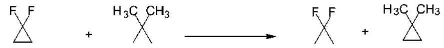
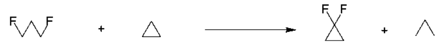
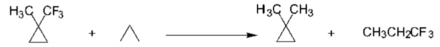
(18) NIST *Standard Reference Database*, Number 69, Nov 1998 (http://webbook.nist.gov/chemistry.)

(19) (a) In general, the G2 BDE's are about 2 kcal/mol higher in energy than the experimental C−H (99.4 ± 0.5 kcal/mol) and C−C (86.2 ± 0.6 kcal/mol) bond dissociation energies for propane. (b) Johnson, W. T. G.; Borden, W. T.; *J. Am. Chem. Soc.* **1997**, *193*, 5930.

Table 2. Homodesmotic Reaction Energies for Estimating the Effects of Methyl, Fluorine, Oxygen, and Trifluoromethyl Substitution on the Strain Energy of Cyclopropanes (G2(MP2) Calculations)

No.	Reaction	SE G2(MP2) kcal/mol	ΔE kcal/mol
	methyl substitution		
1.		27.4	
2a.		27.2	
2b.			-0.2[a]
3.		23.7	
	fluorine substitution		
4a.		40.7	
4b.		20.5	
5a.			-18.7[b]
5b.			-9.9[b]
5c.			-6.6[b]
5d.			-5.3[a]
6a.			-13.3[a]
6b.			-13.5[a]
7.			-6.8[a]
	hydroxyl substitution		
8.		34.5[c] 36.1[d]	
9a.			-12.4[c] -4.6[d]
9b.			-7.1[c] -8.7[d]
	trifluoromethyl substitution		
10.			-5.1
11a.			-0.8
11b.			-0.6

[a] Provides the relative SE based upon different substitution patterns. [b] Decrease in energy associated with the change in the substitution pattern of the acyclic reference compounds. [c] 1,1-Dihydroxycyclopropane and $(CH_3)_2C(OH)_2$ are taken as global minima with internal H-bonding. [d] 1,1-Dihydroxycyclopropane and $(CH_3)_2C(OH)_2$ have C_S geometry, and there are no H-bonding intramolecular interactions.

troversy concerning the fact that three- and four-membered ring hydrocarbons have essentially the same SE can be placed on a more quantitative basis. The G2 BDEs for the C−H bonds in C_3, C_4 and C_5 cyclic hydrocarbons are 110.3, 101.9, and 97.8 kcal/mol suggesting that the greater C−C−C angular strain in cyclopropane is offset by its greatly increased C−H bond energies. Since alkyl-substituted small rings in complex natural products are the rule rather than the exception, the effective strain energy (ESE) in such molecules derived from the prediction of the change in internal energy for a particular chemical transformation is more useful to the experimentalist (e.g., the rational design of a total synthesis) than the intrinsic strain energy (ISE) based upon some hypothetical reference hydrocarbon.

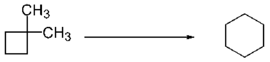
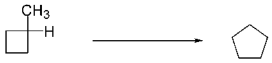
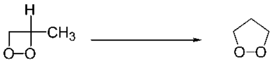
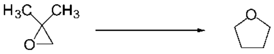
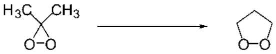
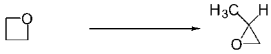
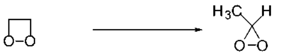
Dissection of three propanes into cyclopropane and three ethanes, homodesmotic reaction 1 in Table 2,[4a] gives an ISE for cyclopropane of 27.4 kcal/mol at G2 and 27.3 kcal/mol at G2(MP2).

The effective strain energy of 1,1-dimethylcyclopropane (27.2 kcal/mol, G2(MP2)), relative to the branched hydrocarbon neopentane (2,2-dimethylpropane) is essentially indistinguishable from that of cyclopropane itself (reactions 2a,b). The SE of 1,1-dimethylcyclopropane by the cyclization method[8] with, *branched reference compound* 2,2-dimethylpropane (neopentane) is predicted to be 28.0 kcal/mol, in excellent agreement with homodesmotic reaction 2a (Table 2). Thus, methyl groups appear to have little impact upon the *relative* strain energies of cyclopropanes as shown by the thermoneutral exchange of methyl groups from the acyclic reference compound with cyclopropane (reaction 2b).

However, attempts to predict the SE of alkyl-substituted cyclopropanes from unbranched or linear hydrocarbon reference compounds presents a unique problem. For example, the formal reaction dimethylcyclopropane + 3 ethane = 2 propane + *n*-pentane suggests a SE of only 21.9 kcal/mol. The formal reaction of 5 cyclohexane = 6 dimethylcyclopropanes also gives a SE for 1,1-dimethylcyclopropane of only 21.1 kcal/mol. Another estimate for the *relative* SE of 1,1-dimethylcyclopropane (21 kcal/mol relative to cyclohexane) comes from its total energy difference from isomeric cyclopentane (14.8 kcal/mol, Table 3) that may be quite accurately related to reference compound cyclohexane ($\Delta SE = 5.9$ kcal/mol). The hypothetical expansion-rearrangement of dimethycyclopropane to cyclohexane with one CH_2 energy equivalent[8] also predicts a SE = 20.7 kcal/mol.

The total energies (G2) of *cis*- and *trans*-1,2-dimethylcyclopropane are 2.7 and 1.3 kcal/mol higher in energy (Table S1) than the gem-disubstituted cyclopropane, supporting the basic premise that all three dimethyl cyclopropanes have a significantly lower *predicted* strain energy than their parent *relative to the more traditional all-anti- linear hydrocarbon*. The major point to be made is that *gem*-dimethyl substitution on a cyclopropane ring imparts a thermodynamic stability of about 6 kcal/mol, relative to a linear reference molecule. This is due not only to the strong bond dissociation energies (BDE) of the C−H bonds of the cyclopropane ring (BDE = 110.3 kcal/mol) but is also a consequence of relatively strong methyl−cyclopropane CH_3−C bonds (97.1 kcal/mol). In this particular case, the stability of dimethylcyclopropane *is not* due to strong methyl C−H bonds, as noted above for neopentane, since the methyl C−H BDE of methylcyclopropane is only 98.0 kcal/mol; a value identical to the *sec*-C−H BDE of the reference compound propane. Irrespective of the philosophical argument of the predicted strain energy, these thermodynamic differences can have a significant impact upon the chemistry of alkyl-substituted cyclopropanes. For example, ring opening of a *gem*-dimethyl cyclopropane to an acyclic fragment maintaining this substitution pattern could be accompanied by as much as 27 kcal/mol relief of strain energy.

Table 3. Relative Energies (kcal/mol) of Isomeric Cyclic Compounds

	G2(MP2)	G2
	-18.3	
 15	-11.4	
 10	-11.8	
	-16.0	-16.0
 9	-14.8	-14.7
	-14.8	-14.8
 7 6	-9.0	-9.7
 2 9	3.2	3.4 $1.6^{a)}$ $0.5^{b)}$
	-0.70	-0.70
 5 4	-3.7	-3.8
 8 3	-16.0	-16.3
 2	-18.2	-18.0

[a] At the QCISD(T)/6-31G*//QCISD/6-31G* level [b] At the QCISD(T)/6-31+G*//B3LYP/6-311+G(3df,2p) level.

However, in a synthetic sequence, conversion of a linear fragment to a *gem*-dimethyl cyclopropane should only increase the internal or ESE by up to 21 kcal/mol.

The calculated SE of cyclohexane itself is 2 kcal/mol relative to the all-anti *n*-hexane.[7a,8] The G2(MP2) energy of all-gauche *n*-hexane, with three *gauche* interactions, is only 1.3 kcal/mol higher in energy than the al*l-anti*-hydrocarbon. The experimental SE of cyclopentane (6.2 kcal/mol) is in good agreement with the $\Delta SE = 5.9$ kcal/mol based upon elimination of a CH_2 fragment (39.22547 au)[8] from the cyclic reference compound, cyclohexane. The SE of cyclopentane may also be estimated from the formal reaction, 5 cyclohexane = 6 cyclopentane (6.2 kcal/mol). At the G2 level, the SE of cyclobutane (26.9 kcal/mol) and cyclopropane (28.2 kcal/mol) relative to their *acyclic* counterparts may also be obtained by cyclization of the corresponding all-*anti*-acyclic C_4 and C_3 hydrocarbons using the $E_{corr} = 1.17956$ au.[8]

The estimated SE of cyclobutane, relative to cyclohexane as the reference compound, is 25.6 kcal/mol based upon the formal reaction*:* 2 cyclohexane = 3 cyclobutane. The experimental strain energy of cyclobutane is reported to be 26.5 kcal/mol.[7] The SE of 1,1-dimethycyclobutane is reduced to 23.5 kcal/mol (G2) as estimated from reaction 3 (Table 2) and 23.0 from the cyclization of 2,2-dimethylbutane ($E_{corr} = 1.18192$ au).[8] However, the SE of 1,1-dimethylcyclobutane is further reduced to 18.3 kcal/mol (G2(MP2)) relative to the total energy of its isomer, cyclohexane, reflecting the *gem*-dimethyl stabilization noted above (Table 3). This is also due to a reduction in angle strain since the $C-CH_3$ bonds in methylcyclobutane (90.8 kcal/mol) are considerably weaker than that of methylcyclopropane (98.5 kcal/mol). Similarly the SE of methylcyclobutane is reduced as shown by it relative energy with cyclopentane (Table 3, ΔE =16.0 kcal/mol). The SEs for substituted hydrocarbons derived from a comparison of the total energies of isomers is clearly a more accurate method for estimating a strain energy relative to a cyclic reference compound (e.g. cyclohexane) than the use of homodesmotic reactions.

The general applicability of this concept is further demonstrated by the hydrogenation of the C−C bonds of a series of cyclic hydrocarbons (Table 4).

The SE of cyclohexane is calculated to be 2.2 kcal/mol relative to *n*-hexane. However, we present the SE in Table 4 relative to cyclohexane for the sake of internal consistency. The agreement with experiment is ±1−2 kcal/mol depending upon the choice of the reference compound. The reduction in SE as a consequence of alkyl substitution is evident, but the necessity to maintain group equivalency with the same number of and types of C−H bonds is also demonstrated. The ISE of substituted cyclopropanes and cyclobutanes, relative to an all-*anti*-reference compound, will be reduced upon formation of the more highly branched positional isomer. Significantly, the ESE relative to a branched hydrocarbon, where the fully formed methyl group is already present in the reference compound, will be comparable in magnitude to the anticipated strain energy of simple unsubstituted cyclic molecules. For example, the energy of hydrogenation of cyclopropane and 1,1-dimethylcyclopropane are indistinguishable, suggesting that both have the same SE. By convention, both of these molecules have the same SE = 27.5 kcal/mol. However, from a pragmatic perspective, the experimentalist should not lose sight of the fact that while the SE of cyclopropane and cyclopentane differ by 21 kcal/mol, the total energy of 1,1-dimethycyclopropane differs from that of cyclopentane by only 14.8 kcal/mol. This basic principle is expressed by the relative energies given in Figure 1 that provides a measure of the thermodynamic stability of more highly branched regioisomers.

(b) Fluorine Substitutents. In general, fluorine strongly prefers to be bonded to carbon orbitals having high p-character. In a seminal study, Borden[20a] suggested that the low-lying C−F antibonding orbitals cause the CF_2 group to act as a net π-electron acceptor. Bond polarization and hybridization changes can account for the energetic and structural effects that arise from substitution with highly electronegative atoms. It was further suggested that geminal fluorines increase the SE in cyclopropane rings; a suggestion consistent with heats of hydrogenation which indicated a thermodynamic increment of 12−14 kcal/mol due to the geminal fluorine substitution. We find an increase in the energy of hydrogenation of 13.4 kcal/mol (Table 4) greater than that of cyclopropane itself, a value in excellent agreement

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(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) For enthalpy values at the MP2/6-311+G*//MP2/6-31G* and B3LYP/6-311+G* levels, see: Wiberg, K. B.; and Marquez, M. *J. Am Chem. Soc.* **1998**, *120*, 2932. (c) Greenberg, A.; Liebman, J.; Dolbier, W. R., Jr.; Medinger, K. S.; Skancke, A. *Tetrahedron* **1983**, *39*, 1533.

Table 4. Energies of Hydrogenation (Δ*E*, kcal/mol) of Cyclic Hydrocarbons and Strain Energies Relative to Cyclohexane at the G2 Level of Theory (SE_{rel}). Experimental Strain Energies (SE_{exp}) Are Given in Bold

C−C bond cleavage (H_2) reaction	Δ*E*	$SE_{rel.}$, **SE_{exp}**[a]
hexane → 2 propane	−8.28	−2.17[b]
cyclohexane → *n*-hexane (anti)	−10.45	0.00, **0.00**
cyclopentane → *n*-pentane (anti)	−16.29	5.84, **6.20**
methylcyclopentane → 2-methylpentane	−15.33	4.88
cyclobutane → *n*-butane	−35.25	24.80, **26.50**
methylcyclobutane → 2-methylbutane	−33.80	23.35
methylcyclobutane → *n*-pentane	−32.30	21.85
1,1-dimethylcyclobutane → 2-methylpentane	−30.04[c]	19.79[c]
1,1-dimethylcyclobutane → 2,2-dimethylbutane	−32.62[c]	22.37[c]
cyclopropane → propane	−36.58	26.12, **27.50**
methylcyclopropane → isobutane	−36.54	26.09
methylcyclopropane → *n*-butane	−34.55	24.10
1,1-dimethylcyclopropane → 2,2-dimethylpropane	−36.28	25.83
1,1-dimethycyclopropane → 2-methylbutane	−32.63	22.1
1,1-difluorocyclopropane → 2,2-difluoropropane	−49.98	39.5[d]
1,1-dihydroxycyclopropane → 2,2-dihydroxypropane	−43.66	33.2[d]

[a] See ref 7. [b] For the SE relative to the acyclic reference hexane, add 2.17 kcal/mol to each of the SE values given. [c] G2MP2 values. [d] SE is based upon relative energy ΔΔ*E* (kcal/mol) to cyclopropane hydrogenation and calculated strain energy of the cyclopropane (26.12 kcal/mol).

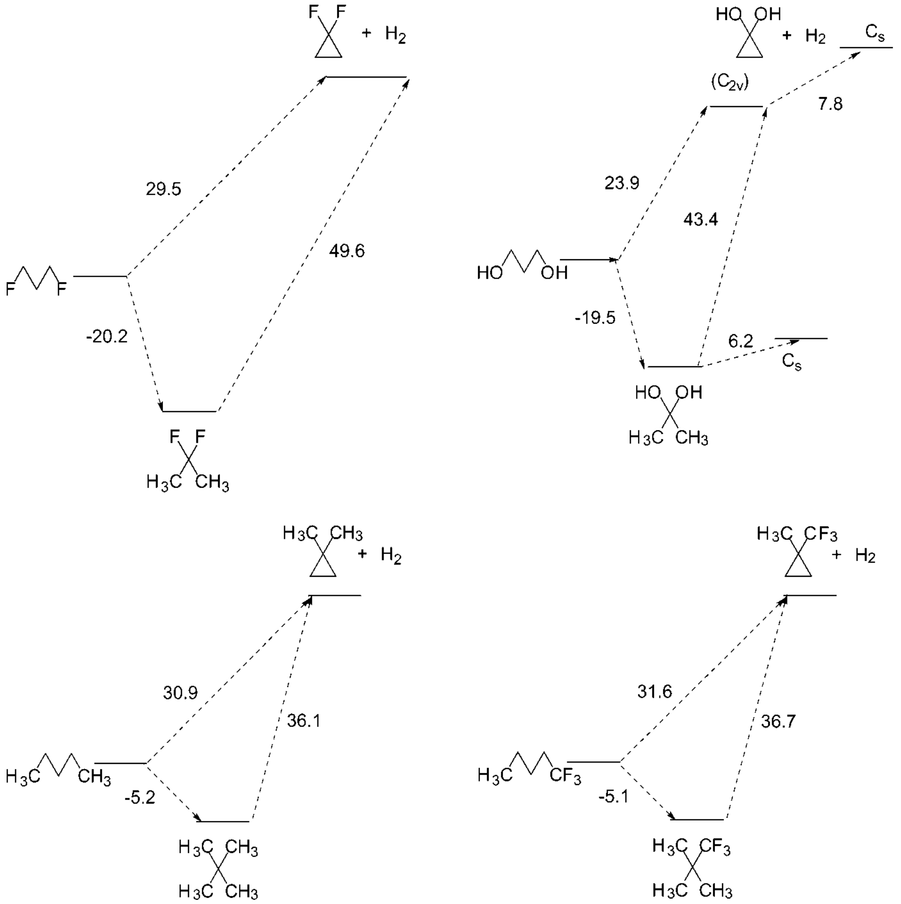


Figure 1. Relative Energies of Isomeric Acyclic and Cyclic Substituted Cyclopropanes (G2(MP2), kcal/mol).

with the SE predicted below of 40.7 kcal/mol based upon homodesmotic reaction 4a. Wiberg[20b] also demonstrated that methyl substitution leads to stabilization of methylene fluoride (CH_2F_2), while fluorine substitution on cyclopropane results in destabilization. The change from ≈sp^3 hybridization in propane to ≈sp^2 in cyclopropane is associated with a strong destabilizing effect of the C−F bond. However, fluorine would rather substitute the highly strained alkene, cyclopropene, than cyclopropane by 10 kcal/mol[20c] making it evident that each type of cyclic molecule must be examined independently.

Upon the basis of the observation that the isomerization of 1,3-difluoropropane to 2,2-difluoropropane is attended by a decrease in energy of 20.2 kcal/mol at G2(MP2) (Figure 1), we anticipated a much greater impact of *gem*-difluoro substitution on the SE of cyclopropanes than *gem*-dimethyl substitution. The homodesmotic reaction involving 2,2-difluoropropane giving 1,1-difluorocyclopropane (reaction 4a, Table 2) predicts an effective strain energy (ESE = 40.7 kcal/mol) that is 13.5 kcal/mol higher than that of its parent cyclopropane, reflecting the destabilizing effect of difluoro substitution on a three-membered ring. However, when the strain energy of 1,1-difluorocyclopropane is measured relative to the all-*anti*-1,3-difluoropropane, the ISE is predicted to be only 20.5 kcal/mol (reaction 4b, G2(MP2)) as a consequence of the higher energy of the 1,3-difluoro reference compound (ΔE = 20.2 kcal/mol, G2(MP2), Figure 1). A comparison of the influence of the *relative* energies of this series of acyclic reference compounds on the energetics of ring closure is also shown in Figure 1. Perhaps the most relevant point to be made, from a chemical perspective, is that the ring opening of a difluorocyclopropyl CF_2 adduct could be attended by the liberation of up too 41 kcal/mol; a source of pent-up internal energy that can potentially be utilized synthetically.

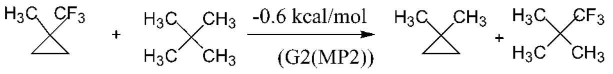
The greater stability of the 2,2-difluoro isomer may be rationalized on the basis of its increasing BDEs. While the C−F bond energies (ΔE, Table 1) of CH_3-F, CH_3CH_2-F, and $CH_3CH_2CH_2-F$ increase somewhat with increasing substitution (110.6, 114.2, and 114.8 kcal/mol), the C−F bonds in 2,2-difluoropropane (124.4 kcal/mol) are considerably stronger, accounting for essentially all of the isomerization energy. The C−H BDEs of the 2,2-isomer (105.7 kcal/mol) are also greater than those of 1,3-difluoropropane (100.1 and 103.2 kcal/mol).

While fluorine prefers to be attached to a carbon bearing other carbons (reaction 5a)[20] even more so than a methyl group (reaction 5b), it clearly prefers not to reside on a cyclopropane ring (reactions 6a and 6b) unless the precursor is 1,3-difluoropropane (reaction 7) or CH_2F_2 (reaction 5d) as evidenced by the series of homodesmotic reactions given in Table 2. The effect of replacing hydrogen at CH_2 groups by fluorine is exothermic (reaction 5a) as is the formation of carbon tetrafluoride (reaction 5c). Reaction 6a indicates that fluorine prefers to be attached to propane rather than cyclopropane by 13.3 kcal/mol, and this preference for bonding to a carbon with higher p-character is directly translated to the strain energy in this cyclic molecule. Consistent with this trend replacement of *gem*-dimethyl with *gem*-difluoro substitution in propane (reaction 5b) is favored by 9.9 kcal/mol. Thus, isomerization of an acyclic 1,3-difluoride to a *gem*-difluoride is favored by 20 kcal/mol (Figure 1) while this substitution pattern in a cyclopropane is destabilized by 13.3 kcal/mol (reaction 6a); the net stabilization (6.8 kcal/mol, G2(MP2)) for this overall transformation is described by reaction 7.

The source of the destabilization of the CF_2 group in a cyclopropane is more problematic. It is clearly not due to diminished bond energies. The C−F bond energy in 1,1-difluorocyclopropane is exceptionally high at 126.1 kcal/mol as are the cyclopropyl C−H bonds (111.7 kcal/mol). The cyclopropyl C−H bond energies in 1,1-dimethylcyclopropane are 108.9 kcal/mol. Angular distortion is one source of destabilization since the C−C−C angles in 2,2-difluoropropane must contract from 116.7 to 63.3°. The F−C−F angle in 1,1-difluorocyclopropane expands from 106.0 to 109.8°. Another major factor is the effective change in hybridization at adjacent carbon[20a] due to the geminal CF_2 group.

(c) Oxygen Substitutents. In assessing the SE inherent to the most commonly used dioxirane, DMDO, the effects of *gem*-dioxa substitution in both acyclic and cyclic hydrocarbons become relevant. Intuitively, an oxidant such as DMDO that incorporates both *gem*-dimethyl and *gem*-dioxa stabilization should exhibit atypical thermodynamic stability for a cyclic peroxide. Dimerization/combination of a series of dioxiranes with cyclopropane predict the SE of DMDO to be 7 kcal/mol lower than that of the parent dioxirane (DO) that has SE $\approx$ 18 and 14 kcal/mol less than that of difluorodioxirane (DFDO).[8] As anticipated from the behavior of two electronegative fluorine substitutents on propane, the energy of 2,2-dihydroxypropane is 19.7 kcal/mol lower in energy than its isomer 1,3-propanediol (Figure 1). The C_{2V} isomer of 1,1-dihydroxycyclopropane is 7.8 kcal/mol lower in energy than the C_S isomer further pointing to the potential dilemma introduced by the presence of intramolecular hydrogen bonding or the anomeric effect[21] as compared to *gem*-diol reference 1,3-propanediol (Figure 1).[22a] In the absence of intramolecular H-bonding, where both diols are restricted to C_S symmetry, the predicted SE of 1,1-dihydroxycyclopropane is 36−45 kcal/mol (according to Figure 1 and eq 9b in Table 2). Upon the basis of its energy of hydrogenation (Table 4), its SE should be 7.1 kcal/mol greater than that of cyclopropane. The effect of oxygen substitutents on the stability of a cyclopropane is comparable to that observed for 1,1-difluoro substitution (reactions 6a and 6b). Thus, we must attribute the remarkably low strain energy of DMDO, at least in part, to the combined thermodynamic influence of geminal substitution at tetrahedral carbon by *both* oxygen and carbon.

(d) Trifluoromethyl Substitutents. The isomerization of 1,1,1-trifluoropentane to the more highly substituted positional isomer 2-methyl-2-trifluoromethylpropane (reaction 10, Table 2) liberates 5.1 kcal/mol (G2(MP2), Figure 1). This surprisingly small stabilization energy is essentially the same as that observed for the isomerization of *n*-pentane to neopentane (ΔE = −5.2 kcal/mol (G2)). A relatively minor effect of CF_3 substitution on a cyclopropane ring is noted in reactions 11a and 11b where exchange of CH_3 and CF_3 groups has no meaningful impact upon the thermodynamic stability of cyclopropanes. This is quite surprising since the $C-CH_3$ bond (97.4 kcal/mol, G2MP2) in 1,1-dimethylcyclopropane is considerably weaker than the corresponding $C-CF_3$ (112.3 kcal/mol, G2MP2) bond. A typical acyclic $C-CF_3$ bond strength is 104−105 kcal/mol. These combined data strongly suggest that the inductive effect of a highly electron-withdrawing group such as CF_3 should exert about the same influence on the stability of cyclopropanes as a methyl group (Figure 1). The SE of methyl(trifluoromethyl)dioxirane (TFDO) has been estimated to be only 1 kcal/mol greater than that of DO which displays an SE approximately 8 kcal/mol more strained than DMDO, a value quite consistent with a relative reactivity 10^3 greater than DMDO.[23]



In contrast, the stabilizing influence of gem-disubstitution of electronegative elements such as oxygen and fluorine on a cyclopropane can potentially be quite large. In general, when the stabilizing influence of geminal alkyl disubstitution is already present in the acyclic reference compound, then strain energies will be com-

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[21] (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.

parable to that of the unsubstituted three-membered ring. These collective observations suggest that dimethyl, difluoro, and trifluoromethyl substitution exerts approximately the same thermodynamic influence on a dioxirane ring as it does on a cyclopropane ring. A series of homodesmotic reactions that are not exactly balanced but yet give an approximate energetics of substitution patterns are given in Supporting Information (Table S4).

II. The Effect of Substitutents on the Strain Energy of Epoxides. The SE of oxiranes is also reduced by the influence of alkyl substitutents. The epoxides derived from the oxidation of propene, *E*-2-butene and isobutylene serve as excellent examples of this principle. A comparison of the total energy of propylene oxide **4** (Table 3) with that of its isomeric four-membered ring ether, oxetane **5**, suggests a SE (21 kcal/mol) for this methyl-substituted epoxide that is 3.8 kcal/mol less than that of isomeric oxetane (SE = 24.7 kcal/mol[7]). Likewise, the total energy of isobutylene oxide **7** is only 9.7 kcal/mol higher in energy than its isomer **6** (THF), predicting a reduction in the SE of this dimethyl substituted epoxide to ≈15 kcal/mol. The 1,2-dimethyl oxiranes derived from *E*- and *Z*-2-butene differ in energy by only 1.3 kcal/mol, and the latter epoxide is only slightly higher in energy (0.5 kcal/mol) than isobutylene oxide. The SE of oxetane (SE = 24.7 kcal/mol) is also reduced by alkyl substitution as evidenced by the isomerization energy of 2,2-dimethyloxetane to tetrahydropyran (−11.4 kcal/mol, Table 3). Thus, epoxides enjoy the same stabilizing influence (≈6−10 kcal/mol) of methyl group substitution as that noted for cyclopropane, cyclobutane, and dioxiranes.

A qualitative estimate of the relative stability of oxiranes may also be gleaned from comparison of their energies (ΔE) of hydrogenation of the C−C bond of the oxirane ring to produce the corresponding ether. The formal addition of H_2 to ethylene oxide ($\Delta E = -29.76$ kcal/mol), propylene oxide ($\Delta E = -27.89$ kcal/mol), and isobutylene oxide ($\Delta E = -25.46$ kcal/mol) show the stabilizing influence of each additional methyl group. The $\Delta\Delta$Es would be even greater when corrected for the differences in BDE of the primary versus *tert*-C−H bonds in the resulting products.

III. Strain Energies from Group Equivalent Reactions. An improved method for predicting the ring strain energies of simple unsubstituted molecules was suggested by Bachrach that utilized group equivalent reactions[5] that are homodesmotic and also conserve the chemical group equivalency (eq 3). This method gave strain energies that were systematically *higher* than those that simply used homodesmotic reactions.

$$\overline{(\mathrm{CH_2})_{n-1} - \mathrm{O}} + (n-2)\,\mathrm{CH_3CH_3} + 2\mathrm{CH_3OH} \rightarrow \mathrm{CH_3OCH_3} + (n-3)\,\mathrm{CH_3CH_2CH_3} + 2\mathrm{CH_3CH_2OH} \tag{3}$$

The two molecules of methanol and two molecules of ethanol serve to balance the reaction and conserve equivalent groups as demonstrated for the cyclic four-membered ring ether, oxetane (eq 4). At the G2 level the SE for oxetane is calculated to be 24.9 kcal/mol. The experimental value is 24.7 kcal/mol.[7] In general, the SE for cyclic hydrocarbons, ethers, and amines calculated by this method[8] are in excellent agreement with experiment.[7]

$$\overline{(\mathrm{CH_2})_3 - \mathrm{O}} + 2\,\mathrm{CH_3CH_3} + 2\mathrm{CH_3OH} \rightarrow \mathrm{CH_3OCH_3} + \mathrm{CH_3CH_2CH_3} + 2\mathrm{CH_3CH_2OH} \tag{4}$$

Due to the geminal dioxa substitution pattern in the reference compounds for dioxiranes there are serious energetic consequences derived from the conformational aspects pertaining to the anomeric effect.[21] Problems also arise due to the markedly different BDEs for the different types of C−O bonds. For example, the C−O bond in CH_3O-CH_3 (85.1 kcal/mol) differs substantially from that when a peroxo bond is involved (CH_3OO-CH_3, 68.8 kcal/mol).

IV. Formal Reactions Providing Estimated SE for Cyclic Peroxides

(A) DO(**1**) + HOOH + 2 $CH_3OH \rightarrow$
2 CH_3OOH + $CH_2(OH)_2$ −19.1 kcal/mol (G2)

(B) DO(**1**) + 2 $CH_3OCH_3 \rightarrow$
CH_3O-OCH_3 + $CH_3OCH_2OCH_3$ −19.0 kcal/mol (G2)

(C) DMDO(**2**) + 2 $CH_3OCH_3 \rightarrow$
$(CH_3O)_2C(CH3)_2$+CH_3OOCH_3 −10.2 kcal/mol (G2)

(D) DMDO(**2**) + $CH_3CH_2CH_3$ + 2 $CH_3OH \rightarrow$
CH_3O-OCH_3 +2 $(CH_3)_2CHOH$ −11.1 kcal/mol (G2(MP2))

(E) 1,2-dioxetane (**8**) + CH_3CH_3 + 2 $CH_3OH \rightarrow$
CH_3O-OCH_3 + 2 CH_3CH_2OH −26.7 kcal/mol (G2)

(F) 1,2-dioxetane (**8**) + 2 $CH_3OCH_3 \rightarrow$
$CH_3OCH_2CH_2OCH_3$ + CH_3OOCH_3 −26.0 kcal/mol (G2)

(G) 1,2-dioxetane (**8**) + 2 $CH_3CH_2CH_3 \rightarrow$
$CH_3CH_2O-OCH_2CH_3$ + $CH_3CH_2CH_2CH_3$ − 27. 6 kcal/mol (G2)

(H) 1,2-dioxolane (**9**) + 2 $CH_3OH \rightarrow$
$HOCH_2CH_2CH_2OH$ + CH_3OOCH_3 −4.8 kcal/mol (G2)

(I) 1,2-dioxane (**10**) + CH_3CH_3 + 2 $CH_3OH \rightarrow$
CH_3O-OCH_3 + $2CH_3CH_2CH_2OH$ −1.9 kcal/mol (G2(MP2))

Adaptation of chemical group equivalency eq 3 provided predicted strain energies[8] for dioxirane (DO) that are lower than we had anticipated initially (reaction A). In an effort to eliminate any potential intramolecular

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[22] (a) We have located three stationary points for methanediol, a structure (global minimum) with the *anti*-directed hydrogens (C_{2V}), a local minimum with the syn-hydrogens and a C_S structure (a first-order saddle point). They have 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 calculated $\Delta H_{f(298)}$ for DMDO (−26.1 kcal/mol) and experimental heats of formation[18] for CH_3OH (−48.0 kcal/mol), $HOCH_2CH_2CH_2OH$ (−97.61 kcal/mol), and CH_3OOCH_3 (−30.0 kcal/mol) give a SE of 5.5 kcal/mol.

[23] For reviews, see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335; and references therein. (d) Adam, W.; Hadjiarapoglou, L. P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed., Wiley: New York, 1992; p 195. (e) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811.

hydrogen bonding interactions[22a] associated with $CH_2(OH)_2$, we used dimethyoxymethane (reaction B) and also predict an SE ≈ 19 kcal/mol for DO. These SE estimates for DO only differ slightly from those based upon the dimerization protocol (17.6, 19.6 kcal/mol) and the CH_2/O insertion method (15 kcal/mol).[8] An adaptation of these methods to the SE of DMDO (formal reactions C and D) provides an estimated (G2MP2) strain energy for *gem*-dimethyl DMDO (10−11 kcal/mol) that is quite close to that predicted by the dimerization method (10.6 kcal/mol)[8] despite the lack of group equivalency. This ΔSE value is also in quite good agreement with a $\Delta SE = 7$ kcal/mol based upon the dimerization method.[8] Thus, the SE of DMDO has been substantially reduced by this geminal dimethyl stabilization effect.

A striking example of substitutent effects comes from a homodesmotic reaction using an unbranched reference compound that predicts a SE of only 1.3 kcal/mol for DMDO.[22c]

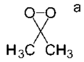
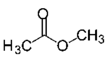
$$\mathrm{DMDO} + 2\mathrm{CH_3OH} \rightarrow \mathrm{CH_3O{-}OCH_3} + \mathrm{HO{-}CH_2CH_2CH_2{-}OH} - 1.3\ \mathrm{kcal/mol} \quad (5)$$

Since 2,2-dihydroxypropane is 19.5 kcal/mol lower in energy than its the 1,3-diol isomer at the G2 level of theory (Figure 1), the predicted SE is lowered accordingly. Thus, as noted above for the series of homodesmotic reactions with cyclopropanes, at the very minimum the pattern of methyl and fluorine group substitution must be balanced on both sides of the equation. The surprisingly large difference in energy between the 1,3-difluoropropane and 1,3-propanediol and their respective 2,2-isomers demonstrates in a rather dramatic fashion (Figure 1) the importance of the choice of the acyclic reference compound when attempting to predict ring strain energies. The thermodynamic effect of gem-disubstitution must be recognized, and the reference compound in each case has to be explicitly specified in order for the estimated SE to have chemical relevance.

Extension of the group equivalency method to four-, five-, and six-membered cyclic peroxides, where the reference compounds do not have the requisite 1,3-dioxa substitution pattern, gave strain energies in excellent agreement with those reported earlier.[8] The estimated SE of 1,2-dioxetane **8** (reactions E, F, and G, 26.8 kcal/mol) is comparable to that of cyclobutane (26.5 kcal/mol). The algorithm in eq 3[5] yields group equivalent reactions for estimating SE that typically uses the smallest possible reference molecules. This equation, however, is not unique, and balanced reactions using larger reference molecules, but not necessarily alcohols, are also internally consistent.[5] In general, using larger reference molecules systematically produces SE that differs by ≈1 kcal/mol as exemplified by comparison of reactions E and G for 1,2-dioxetane **8.** The SE of 1,2-dioxolane **9** is also in excellent agreement with the other methods we have presented.[8] The SE, 1.9 kcal/mol, of the six-membered ring reference peroxide **10** (reaction I**)** is approximately the same as that calculated[7a] for cyclohexane (2.2 kcal/mol).[8]

V. The Relative Stability of DMDO and 1,2-Dioxolane. The compilation of G2 and G2(MP2) total energies and their energy equivalents make it possible to perform direct comparisons among the entire series of isomeric cyclic molecules. Perhaps the most surprising example of this theoretical data comes from a comparison of the SE of DMDO with that of its isomer 1,2-dioxolane (1,2-dioxacyclopentane). The SE of five-membered ring peroxide **9** is predicted to be 4.8 kcal/mol greater than that of the acyclic reference compound diethyl peroxide and 21.0 kcal/mol less than that of the next lowest homologous four-membered ring peroxide, 1,2-dioxetane **8**.[8] The total energy of dimethyldioxirane **2** at the G2 level of theory is 3.4 kcal/mol *lower* than that of 1,2-dioxolane (Table 3), placing the SE of DMDO ≈ 1−2 kcal/mol above that of the strain-free all-*anti*-reference compound diethyl peroxide. This assessment is also supported by the insertion/contraction protocol recently reported[8] and the above group equivalent reactions, both of which place the SE of isomeric 1,2-dioxolane at 5 kcal/mol. The predicted SE based upon homodesmotic reaction 5 (1.3 kcal/mol) is also based upon unbranched 1,3-propanediol and is entirely consistent with the predicted SE for DMDO relative to isomeric cyclic peroxide, 1,2-dioxolane.

Table 5. Relative Energies ($E_{\mathrm{rel.}}$, kcal/mol) for Isomers of DMDO. Total Energies Are Given in Supporting Information Table S3)

Method	 a **2**	 b **9**	 **11**	 **12**
B3LYP/6-311+G(3df,2p)	0.0	-1.38	-49.03	-78.07
QCISD(T)/6-31+G(d)//B3LYP/6-311+G(3df,2p)	0.0	0.50	-46.50	-73.12
QCISD/6-31G(d)//QCISD/6-31G(d)	0.0	0.79	-46.76	-74.03
QCISD(T)6-31G(d)//QCISD/6-31G(d)	0.0	1.56		
QCISD(T)/6-31+G(d)//QCISD/6-31G(d)	0.0	0.73	-46.05	-72.92
QCISD/6-31+G(d,p)//QCISD/6-31+G(d,p)	0.0	-0.21		
G2(MP2)	0.0	3.21	-44.80	-73.03
G2	0.0	3.44	-44.55	-73.10
G2(MP2) (QCI) [c]	0.0	3.00		
G2 (QCI) [c]	0.0	3.23		
CBS-APNO	0.0	2.59		

[a] The **O−O** bond length for **2** at the QCISD/6-31+G(d,p), QCISD/6-31G(d), MP2, and BLYP levels are 1.527, 1.523, 1.532, and 1.496 Å. [b] The **O−O** bond length for **9** at the QCISD/6-31+G(d,p), QCISD/6-31G(d), MP2, and BLYP levels are 1.465, 1.465, 1.474, and 1.453 Å. [c] G2, G2(MP2) and HF/6-31G(d) frequency calculation on the QCISD/6-31+G(d,p) geometry.

Since G2 energies are derived from MP2/6-31G(d) geometries, and it has been suggested that *f* orbitals are required to get adequate geometries for DO and DFDO,[6a] we also examined the effect of basis set on the relative energies of these two isomeric peroxides. An increase in the basis set gives a decrease in the O−O bond length; thus, we optimized the geometries of both DMDO and 1,2-dioxolane at the B3LYP/6-311+G(3df,2p) level. The latter peroxide is, in fact, predicted to be *more* stable by 1.4 kcal/mol (Table 5).

However, at the QCISD(T)/6-31+G*//B3LYP/6-311+G(3df,2p) level DMDO is 0.5 kcal/mol more stable. Similarly, with geometry optimization at the QCISD/6-31G* and further refinement of this energy at the QCISD(T)/6-31+G* level, DMDO proved to be 1.6 kcal/mol lower in energy. We also optimized both structures at the QCISD/6-31+G(d,p) level and found only a minor change in O−O bond length with 1,2-dioxolane now being 0.2 kcal/mol lower in energy but virtually no change in their relative energies (−3.2 kcal/mol) when the requisite series of G2 calculations (with a HF/6-31G* frequency) were carried out on these QCISD geometries (Table 5). The relative energies of DMDO and dioxolane **9** by the more accurate CBS-APNO[16c] method remained essentially unchanged at −2.6 kcal/mol.

The relative stabilities of DMDO and 1,2-dioxolane can also be supported by experimental heats of formation of isomeric compounds such as 1,3-dioxacyclopentane (**11**) to compare with the calculated $\Delta\Delta H_{f(298)}$ of reaction for their interconversion.[24] The experimental $\Delta H_{f(298)}$ of 1,3-dioxolane **11** (−72.10 kcal/mol) and methyl acetate **12** (−98.00 kcal/mol) can be related to isomeric DMDO by reaction enthalpies calculated at the G2 level. The difference between the experimental ($\Delta\Delta H_{f(298)} = -25.9$ kcal/mol) and calculated[24] ($\Delta\Delta H_{f(298)} = -27.7$ kcal/mol) enthalpies for these two reference compounds gives an indication of the potential error (≈2 kcal/mol) involved in these approximations. A $\Delta H_{f(298)} = -27.0$ for DMDO may be estimated from the experimental $\Delta H_{f(298}$ for 1,3-dioxolane (−72.10 kcal/mol) and the calculated $\Delta H_{(298)}$ =-45.09 kcal/mol ($\Delta H_{f(298}\{1,3\text{-dioxolane}\}_{exp} - \Delta H_{f(298)}$-{DMDO} $=\Delta H_{(298)calcd}$). Similarly, the calculated $\Delta H_{298} = -72.8$ for DMDO → methyl acetate (−98.0 kcal/mol) gives an estimated $\Delta H_{f(298)} = -25.2$ kcal/mol for DMDO. The average of these two values (−26.1 kcal/mol) is in excellent accord with the heat of formation suggested by Cremer[6a] (−25.3 kcal/mol).

From the difference in the experimental $\Delta H_{f(298}$ for 1,3-dioxolane (**11**, −72.10 kcal/mol) and the calculated reaction energy[24] to form its 1,2-isomer ($\Delta H_{(298)} = -47.86$ kcal/mol), the estimated $\Delta H_{f(298)}$ for 1,2-dioxolane **9** is −24.2 kcal/mol. A similar exercise with the $\Delta\Delta H_{f(298)}$ for the reaction CH_3COOCH_3 → 1,2-dioxolane suggests a $\Delta H_{f(298)} = -23.3$ kcal/mol (average = 23.8 kcal/mol). The calculated difference in their heats of formation ($\Delta\Delta H_{f(298)} =$ 2.8 kcal/mol) is in excellent agreement with the difference in the G2 total energies for these two cyclic peroxides given in Table 5 supporting the conclusion based upon experiment that *DMDO is in fact thermodynamically more stable than 1,2-dioxolane* with a G2 total energy difference of −3.4 kcal/mol (MP2 geometry) −3.2 kcal/mol (QCISD/6-31+G(d,p)) geometry, and −2.6 kcal/mol at CBS-APNO (Table 5).

The simple fact that the total energy (G2) of DMDO **2** is *lower* than that of 1,2-dioxolane **9** is a striking observation that demands a unique explanation. Quite obviously the reactivity of this versatile oxidant toward hydrocarbons must be ascribed to reasons other than its strain energy. Since we cannot readily determine the O−O bond dissociation energy (BDE) of a dioxirane, we looked at the BDE of the C−H bonds in DMDO. 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. The BDE for the C−H bond of DMDO are 102.7 kcal/mol and the α and *β* C−H BDE in dioxolane are 96.6 and 102.4 kcal/mol (G2(MP2)). In general, C−H bonds adjacent to oxygen are relatively weak (Table 1). A qualitative estimate of the magnitude of this stabilizing influence can come from a comparison of the C−H bond dissociation energies (BDE) in DMDO versus those in dioxolane; the sum of the C−H bond BDEs in DMDO is 24.7 kcal/mol (ΔH_{298}, G2(MP2)) higher in energy. The strength of the $C-CH_3$ bonds in DMDO likely arise from a stabilizing interaction between the O−O bond and the $C-CH_3$ orbitals since the $C-CH_3$ bond in acyclic reference compound 2,2-dihydroxypropane is only 92.8 kcal/mol.

The thermodynamic stability of DMDO is also a consequence of its relatively strong $C-CH_3$ bonds (BDE = 98.9 kcal/mol). Coincidentally, the $C-CH_3$ bond in methylcyclopropane is also atypically strong (97.1 kcal/mol). However, this effect seems to be specific to a three-membered ring since the $C-CH_3$ BDE in methylcyclobutane is only 92.9 kcal/mol. More importantly, the $C-CH_3$ bond energies for 2,2-dimethyloxetane (87.8 kcal/mol, G2) and 3,3-dimethydioxetane (89.5 kcal/mol, G2-(MP2)) are significantly lower than that in DMDO (98.9 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 internal energy* to within 3.4 kcal/mol of that of dioxolane. It should be recalled that the dimerization method[8] assigns a SE to DMDO of 10.6 kcal/mol *relative to a branched cyclic reference compound* that already possesses the stabilizing influence of the *gem*-dimethyl groups.

We have emphasized strongly the fact that DMDO is thermodynamically more stable than isomeric 1,2-dioxolane (**9**) and that this cyclic peroxide is only modestly strained (SE = 5.1 kcal/mol). However, we should not lose sight of the fact that while the SE of **9** is measured relative to an acyclic peroxide, *both compounds* contain a high-energy peroxide bond. For example, the O−O BDE for CH_3O-OCH_3 is only 39.4 kcal/mol (G2).[9] This point is dramatically emphasized by the fact that isomerization of **9** to its isomeric 1,3-dioxacyclopentane (**11**) is attended by the liberation of 48.0 kcal/mol (Figure 2). The energy difference between dioxetane **8** and its isomeric diether 1,3-dioxacyclobutane (**13**) is 60.0 kcal/mol; even the cyclic six-membered ring reference compound is 49.4 kcal/mol (G2(MP2)) higher than isomeric 1,3-dioxacyclohexane (**14**, Figure 2). These very high-energy differences between isomeric peroxides and diethers are obviously a consequence of weak O−O bonds in the peroxide contrasted by two much stronger C−O bonds in the 1,3-diethers. Insertion of a CH_2 group into DO[8] affording dioxetane **8** suggests a ΔSE of 11 kcal/mol (Figure 2). The SE difference of 21 kcal/mol for dioxetane **8** versus dioxolane **9** is quite consistent with our other data. From this perspective, it does not seem as counterintuitive that the relative stability of DMDO and dioxolane **9** are comparable. Both are high-energy peroxides whose strain energies are calculated *relative to a high-energy acyclic peroxide reference compound* (diethyl peroxide).[8] To place this comparison in perspective, recall that 1,1-dimethylcyclopropane has an ESE of 21 kcal/mol and a total energy that is 14.8 kcal/mol greater than isomeric cyclopentane. DMDO is 2.6 kcal/mol (CBS-APNO) lower in energy than its five-membered ring isomeric peroxide due in part to the additional geminal dioxygen substitution of DMDO. While cyclopentane and dioxolane **9** have vastly different thermodynamic stabilities, they have quite comparable strain energies with the latter peroxide being slightly *less strained* (SE = 5 kcal/mol).

With an established stability of DMDO, its reactivity toward saturated hydrocarbons cannot be attributed

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[24] G2 Enthalpies (298 K) of DMDO (**2**), 1,3-dioxacyclopentane (**11**), 1,2-dioxacyclopentane (**9**), and methyl acetate (**12**) are −267.84210, 267.91396, 267.83770, and 267.95813 au, respectively.

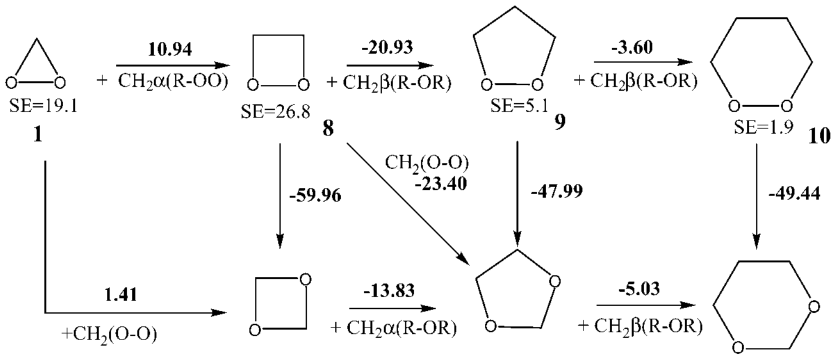
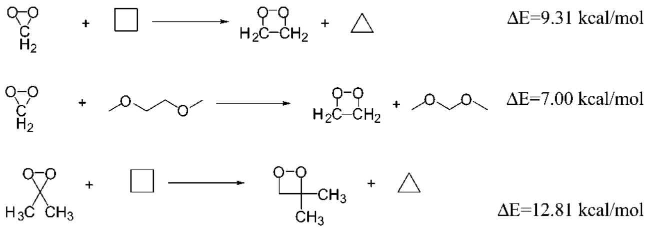


Figure 2. Schematic representation of the energetic consequences of successive ring expansions of DO (**1**) by CH_2 group energy equivalents. All energy differences (kcal/mol) are based upon G2 calculations except for the six-membered 1,2- and 1,3-dioxacyclohexanes which are calculated at the G2MP2 level. The SE values are based upon calculated energetics for n-membered cyclic peroxide expansion to ($n + 1$)-membered cyclic peroxide with one CH_2 group energy equivalent. SE of 1,2-dioxacyclohexane is calculated with respect to diethyl peroxide. For a discussion of CH_2 energy equivalents, see ref 8.

solely to relief of strain energy. If DMDO does open to a singlet diradical[25] along the pathway for abstraction of a hydrogen atom in a concerted insertion reaction, 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 activation barriers for the epoxidation of alkenes by the unstrained peroxy acids and DMDO are quite similar.[15] As reported by Cremer,[6a] 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.[23]

VI. The Relative Energies of Dioxiranes and Dioxetanes. A fundamental enigma that remains to be discussed is the fact that dioxiranes are considerably less strained than their four-membered ring analogues.[1,7] The SE of three-membered ring hydrocarbons, ethers, and amines are all slightly greater than the corresponding four-membered ring compound. 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);[8] 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 7−11 kcal/mol. It is also obvious that dioxetanes have SE 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 cannot be considered a highly strained molecule*! These assertions are further supported by the formal reactions below that demonstrate clearly the lower *relative* SE of dioxirane. This is due solely to their inherent strain energy since the C−H BDE in DO and 1,2-dioxetane are identical (103.7 kcal/mol). Since cyclopropane and cyclobutane have comparable SEs, this is a reasonable comparison although the critical dioxa environment of the methylene groups in dioxetane (**8**) is not maintained. When this is corrected with properly balanced methyl ethers, the predicted difference in the SE of these cyclic peroxides suggests the DO is less strained by 7.0 kcal/mol, a value consistent with the Δ*SE* = 10.8 kcal/mol based upon the totally independent CH_2-extrusion method reported recently.[8] This predicted SE difference widens to 12.8 kcal/mol (G2(MP2)) as methyl substitution is included. Presumably, the C−H BDE of 3,3-dimethyldioxetane is somewhat less than that in DMDO. The comparable SE of dioxetane **8** and cyclobutane is demonstrated by a comparison of the isomerization energies (Table 3) of methyldioxetane to 1,2-dioxolane **9** (−14.7 kcal/mol**)** with methylcyclobutane to cyclopentane (−16.0 kcal/mol).



Dioxiranes are clearly less strained than dioxetanes and this difference in SE cannot merely be ascribed to different reference compounds but is apparently a consequence of a special electronic structure effect peculiar to a three-membered peroxide where inclusion of two heteroatoms *lowers* the strain energy.

Conclusions

The SE of cyclopropanes, cyclobutanes, epoxides, and dioxiranes are reduced by 6−10 kcal/mol by the *gem*-dimethyl stabilization relative to the corresponding unbranched reference compounds.

The stabilization energies for the isomerization, $X-CH_2CH_2CH_2-X \rightarrow CH_3-CX_2-CH_3$, where X= CH_3, OH, and F, are 5.2, 19.5, and 20.2 kcal/mol, respectively. The strain energies of the corresponding gem-disubstituted cyclopropanes, relative to the unbranched 1,3-disubstituted reference compounds are reduced by approximately the same quantity.

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[25] (a) Anglada, J. M.; Bofill, J. M.; Olivella, S.; Solé, A. *J. Phys. Chem. A.* **1998**, *102*, 3398. (b) Cantos, M.; Merchan, M.; Tomas-Vert, F.; Roos, B. O. *Chem. Phys. Lett.* **1994**, *229*, 181, (c) Bach, R. D.; Andrés, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207.

The group equivalent reactions protocol, which conserves the next nearest neighbor bonding concept maintaining the same molecular environment on both sides of the equation, provides a highly reliable method for determining the strain energies of four- to six-membered ring compounds but is less accurate for dioxiranes.

The SE of DMDO is SE $\approx$ 11 kcal/mol with respect to a *gem*-dimethyl reference molecule but only 1−2 kcal/mol relative to a linear or unbranched peroxide. The calculated total energy (G2) of DMDO is 3.4 kcal/mol (−2.6 kcal/mol at CBS-APNO) lower in energy than its isomeric five-membered ring peroxide, 1,2-dioxacyclopentane.

The inherent strain of dioxiranes places the strain energy of these three-membered ring peroxides much lower than cyclopropanes, epoxides, aziridines, and 1,2-dioxetanes. The estimated SE for the parent dioxirane (DO) and DMDO are 18 and 11 kcal/mol.

The SE of 1,2-dioxetane (**8**) is predicted to be 7−11 kcal/mol greater than DO but 21 kcal/mol less than 1,2-dioxolane (**9**) and 25 kcal/mol greater than cyclic reference compound **10**. The reactivity of 1,2-dioxetanes is due to relief of strain energy, but the highly reactive DMDO toward saturated hydrocarbons in hydroxylation reactions is more likely a function of the involvement of disubstituted dioxomethylene singlet states along the reaction pathway. These data greatly impact how we think about the origin of the reactivity of DMDO since we have traditionally regarded it as a “highly strained cyclic peroxide” that can readily oxidize saturated hydrocarbons.

When considering the effect of strain energy upon a chemical transformation, synthetic chemists should give consideration to the change in the substitution pattern as well as the change in ring size.

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Supporting Information Available: Total energies calculated at the G2(MP2) and G2 level of theory (at 0 K) for all compounds, total and relative energies for isomers of DMDO at different levels of theory (Tables S1−S3), a series of homodesmotic reactions that are not exactly balanced but yet give approximate energetics of substitution patterns in dioxiranes (Table S4) and Cartesian coordinates obtained within G2 and G2(MP2) optimizations [MP2(Full)/6-31G(d)]. This material is available free of charge via the Internet at http://pubs.acs.org

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