Thermochemical Studies of Epoxides and Related Compounds

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S *Supporting Information*

ABSTRACT: Gas-phase heats of formation for the four butene oxide isomers are reported. They were obtained by measuring the condensed-phase heat of reduction to the corresponding alcohol using reaction calorimetry. Heats of vaporization were determined and allow gas-phase heats of formation to be obtained. The experimental measurements are

| $\Delta H_f(g)$/kcal mol^{-1} | -33.4 ± 0.6 | -33.4 ± 0.7 | -31.6 ± 0.5 | -27.8 ± 0.4 |
| strain energy | 23.0 | 22.1 | 22.0 | 24.4 |

compared to calculations obtained using a variety of computational methods. Overall, the G3 and CBS-APNO methods agree quite well with the experimental data. The influence of alkyl substituents on epoxide stability is discussed. Comparisons to alkenes, cyclopropanes, aziridines, thiiranes, and phosphiranes are also made. Isodesmic-type reactions were used to determine strain energies of the epoxides and related compounds with various substituents.

INTRODUCTION

Epoxides are strained heterocycles that are encountered throughout chemistry. Epoxides are simple to synthesize and reasonably stable. They react readily, often via reactions that relieve ring strain, such as the addition of a nucleophile to a ring carbon.[1] It is reasonable to think that the reactivity of a specific epoxide is related to its strain, which is likely to be dependent on the number and nature of the substituents on the epoxide ring.

However, there is currently little information on energies and strain in epoxides with alkyl substituents. Gas-phase heats of formation (ΔH_f) are known for oxirane, methyloxirane, and some simple cyclic epoxides,[2−4] though some of these data have high uncertainty. ΔH_f have not been measured for compounds as simple as *cis*- and *trans*-2,3-dimethyloxirane. Isodesmic-type reactions[5] are commonly used to obtain strain energies. This type of analysis relies on the availability of either ΔH_f or high-quality calculations.

An extreme example of the influence of structural variation on epoxide reactivity is the competing mechanisms of base-induced isomerizations of epoxides.[6] Most epoxides react with bulky lithium amides via β-elimination, to generate the allylic alcohol. However, in epoxides presumed to have greater strain, such as cyclopentene oxide and cyclooctene oxide, the bridgehead ring protons are more acidic, and under the same reaction conditions, α-elimination to a carbenoid intermediate[7] takes place instead:
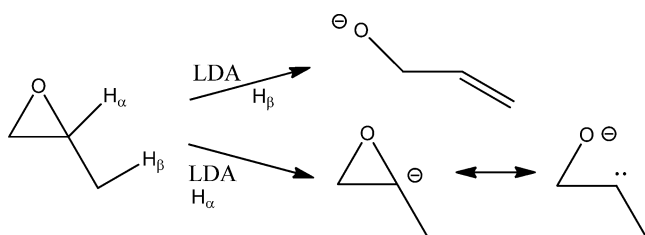
The chemistry of aziridines has expanded greatly in recent years.[1] However, only the ΔH_f of aziridine itself is known,[2] and as such the influence of substituents on the enthalpy and strain of aziridines is not well quantified. Unlike epoxides, aziridines treated with strong bulky base favor α-deprotonation over β-elimination, when nitrogen is substituted with anion-stabilizing substituents.[8] Experimentally, β-elimination has been observed in few cases, such as when α-protons are not present.[9] The enhanced α-deprotonation of aziridines may be due to greater strain.

In this study, a combination of experiment and theory is presented that will expand our knowledge of epoxides. The experiments include reaction calorimetry and ebulliometry, which ultimately allow ΔH_f to be determined. Reaction calorimetry has been carried out to determine the heat of reducing simple epoxides to the corresponding alcohols. Lithium triethylborohydride is an ideal reducing agent; the reaction is rapid at room temperature and gives a quantitative conversion to a well-defined product.[10] In addition, only one hydride is available on the reducing agent. This method has been used previously in a calorimetry study in which aldehydes and ketones were reduced to alcohols.[11] The ΔH_f of the product alcohols are well-known, allowing the epoxide ΔH_f to be obtained from the heat of reduction. Including heats of vaporization (ΔH_v) provides gas-phase results. While combustion calorimetry can also be used to obtain ΔH_f, the technique has drawbacks. Combustion energies tend to be large, on the order of hundreds if not thousands of kilocalories per mole. As such, even highly precise combustion measurements can have large absolute uncertainty. Reaction energies tend to be much smaller, 20−50 kcal mol^{-1}, and smaller error can be obtained. In addition, a variety of computational methods are used to model the reduction enthalpies, some methods with

significantly better success than others. Comparisons to substituted cyclopropanes, alkenes, aziridines, and other heterocycles are also made, and the influence of substituents on the stability and strain energies of the various compounds is discussed.

■ RESULTS AND DISCUSSION

Experimental Studies: Reaction Calorimetry. In the reaction calorimetry experiment, the enthalpy of reaction is determined for the process in which the pure liquid epoxide substrate reacts with lithium triethylborohydride in solution to form the lithium salt of the alcohol, in solution (ΔH_{r1}, eq 1). In a second measurement, the pure liquid alcohol is dissolved in the reaction medium containing the reducing agent, producing the same solvated lithium salt of the alcohol, plus H_2 (ΔH_{r2}, eq 2). Subtracting eq 2 from eq 1 yields the condensed-phase heat of reduction (ΔH_{red}) of pure liquid epoxide to pure liquid alcohol. Lithium triethylborohydride is known to give quantitative reactions with epoxides,[10] with Markovnikov regioselectivity.[12] The reaction is generally rapid at 25.1 °C, the temperature at which the calorimetry experiments were carried out. Triethylene glycol dimethyl ether is used for the solvent; it is high boiling so that the generation of H_2 does not cause solvent to evaporate significantly, which would affect the measured heat of reaction with the alcohol. Heats of reduction of simple aldehydes and ketones to alcohols have previously been determined by reaction calorimetry using this LiEt₃BH method.[11] The literature value for the liquid-phase reduction of acetone to 2-propanol is -16.43 ± 0.10 kcal mol^{-1},[11] and this was reproduced in this study, -16.30 ± 0.12 kcal mol^{-1}. Table 1 presents the results of the calorimetry experiments, each number representing the average of at least four measurements.

Ethyloxirane and *cis*- and *trans*-2,3-dimethyloxiranes reduce to 2-butanol, and 2,2-dimethyloxirane reduces to *tert*-butyl alcohol. The condensed-phase ΔH_f of the epoxides are also tabulated, determined from the ΔH_{red} and the known ΔH_f for the alcohols.[2]

The ΔH_f obtained for methyloxirane in this study matches the literature value. However, the values for ethyloxirane are significantly different. The literature value[13] here is likely to be in error; this study reported ΔH_f for oxirane and methyloxirane that are also 4−5 kcal mol^{-1} more exothermic than the

accepted literature values. Further, high-level computational results (*vide infra*) agree with our value and the accepted literature values for oxirane and methyloxirane. The reductions of *cis*- and *trans*-2,3-dimethyloxirane and the deprotonation reaction of *tert*-butyl alcohol were slower than the ideal 30 min, leading to greater uncertainty in the measurements. Also, *tert*-butyl alcohol is a solid at 25 °C, and the heat of melting is complicated, with several distinct crystalline transitions occurring around room temperature.[14] As such, the calorimetry experiments for this compound were carried out for liquid *tert*-butyl alcohol at 26.1 °C. The error introduced with this 1 °C deviation from standard conditions is expected to be minor and less than the uncertainty due to the phase transitions of the solid and is ignored.

The gas-phase epoxide ΔH_f and ΔH_{red} can be obtained when ΔH_v are known (Table 2). The epoxide ΔH_v were determined

Table 2. Heats of Vaporization and Gas-Phase Enthalpies of Formation and Reduction (kcal mol^{-1})

epoxide	ΔH_v	ΔH_f (g)	ΔH_{red} (g)
methyloxirane	6.67 ± 0.01^a	-22.9 ± 0.2	-42.2 ± 0.2
ethyloxirane	7.98 ± 0.3	-27.8 ± 0.4	-42.2 ± 0.5
cis-2,3-dimethyloxirane	8.11 ± 0.3	-31.6 ± 0.5	-38.4 ± 0.5
trans-2,3-dimethyloxirane	7.90 ± 0.3	-33.4 ± 0.7	-36.6 ± 0.7
2,2-dimethyloxirane	7.39 ± 0.3	-33.4 ± 0.6	-41.3 ± 0.6

^{a}Reference 2.

by ebulliometry. Here, the boiling point is measured at a variety of pressures. The data are fit to the Clausius−Clapeyron equation and corrected to 25.15 °C as previously described.[15] The ΔH_{red} (g) were calculated from the epoxide ΔH_f (g) and alcohol ΔH_f (g) from the literature.[2] A comparison of the ΔH_f (g) of the isomeric epoxides allows their relative stability to be determined. The stability trend is the same as in alkenes, with the *gem*- and *trans*-dimethyl epoxides as the most stable and the monosubstituted isomer as the least stable. These results will be discussed in more detail below and will be compared to other functional groups.

Calculated Heats of Reduction, Heats of Formation, and Substituent Effects. A series of calculations has been carried out to identify the most reliable methods for predicting
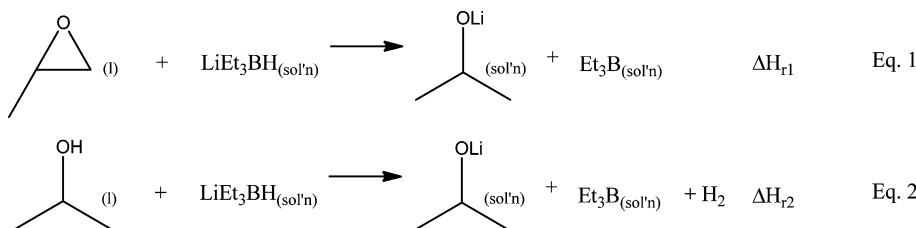
$$\text{(epoxide)}_{(l)} + \text{LiEt}_3\text{B}_{(sol'n)} \longrightarrow \text{(lithium alkoxide)}_{(sol'n)} + \text{Et}_3\text{B}_{(sol'n)} \qquad \Delta H_{r1} \qquad \text{Eq. 1}$$

$$\text{(alcohol)}_{(l)} + \text{LiEt}_3\text{B}_{(sol'n)} \longrightarrow \text{(lithium alkoxide)}_{(sol'n)} + \text{Et}_3\text{B}_{(sol'n)} + \text{H}_2 \quad \Delta H_{r2} \qquad \text{Eq. 2}$$

Table 1. Condensed-Phase Enthalpies of Reduction and Formation of Epoxides (kcal mol^{-1})

epoxide	ΔH_{r1}	ΔH_{r2}	ΔH_{red} (l)	ΔH_f (l)	ΔH_f (l), lit.^{a}
methyloxirane	-53.463 ± 0.086^b	-6.992 ± 0.031	-46.47 ± 0.09	-29.55 ± 0.15	-29.30 ± 0.15
ethyloxirane	-52.707 ± 0.216	-6.636 ± 0.104	-46.07 ± 0.24	-35.80 ± 0.33	-40.46 ± 0.62
cis-2,3-dimethyloxirane	-48.812 ± 0.291	-6.636 ± 0.104	-42.18 ± 0.31	-39.69 ± 0.39	
trans-2,3-dimethyloxirane	-47.185 ± 0.591	-6.636 ± 0.104	-40.55 ± 0.60	-41.32 ± 0.64	
2,2-dimethyloxirane	-46.320 ± 0.230	-1.235 ± 0.371	-45.08 ± 0.44	-40.78 ± 0.48	

^{a}Reference 2. ^{b}Uncertainties are twice the standard deviation from the mean.

Table 3. Gas-Phase Enthalpies of Reduction (kcal mol^{-1})

	ΔH_{red} (g) this study	ΔH_{red} (g) lit.[a]	AM1	RHF/ 3-21G	MP2/ 6-31G*	B3LYP/ 6-31G*	B3LYP/ 6-311++G**	CBS-QB3	G2	G3	CBS-APNO
					Epoxides						
oxirane		−43.66 ± 0.17	−43.9	−55.7	−34.2	−39.1	−43.4	−41.9	−42.2	−43.2	−43.4
methyloxirane	−42.2 ± 0.2	−42.49 ± 0.20	−43.0	−54.8	−36.1	−37.3	−41.8	−41.2	−41.5	−42.4	−42.6
cis-2,3-dimethyloxirane	−38.4 ± 0.5		−42.3	−52.1	−31.9	−33.0	−37.5	−37.1	−37.6	−38.3	−38.4
trans-2,3-dimethyloxirane	−36.6 ± 0.7		−41.5	−50.3	−30.4	−31.6	−36.0	−35.9	−36.3	−37.0	−37.2
2,2-dimethyloxirane	−41.4 ± 0.6		−40.0	−54.4	−35.4	−35.5	−40.1	−40.5	−40.9	−41.7	−41.9
ethyloxirane	−42.2 ± 0.5		−42.2	−54.8	−35.9	−37.1	−41.4	−41.1	−41.4	−42.3	−42.4
mean error, epoxides			1.9	12.9	6.8	5.1	0.7	1.1	0.8	0.3	0.3
					Alkenes						
propene		−29.71 ± 0.21	−19.0	−34.7	−30.8	−31.6	−28.5	−29.1	−29.6	−29.6	−30.6
cis-2-butene		−28.50 ± 0.26	−15.6	−34.0	−29.2	−29.2	−26.5	−27.8	−28.2	−28.4	−29.2
trans-2-butene		−27.37 ± 0.24	−15.6	−32.3	−27.6	−27.8	−25.5	−26.5	−26.8	−27.1	−28.0
2-methylpropene		−28.15 ± 0.20	−16.4	−33.5	−28.8	−28.5	−26.0	−27.3	−25.7	−27.9	−28.8
1-butene		−30.16 ± 0.21	−19.3	−34.6	−30.8	−31.7	−28.6	−29.3	−29.4	−29.7	−30.7
mean error, alkenes			11.6	5.0	0.7	1.0	1.8	0.8	0.8	0.2	0.7
mean error, all			6.3	9.4	4.0	3.3	1.2	1.0	0.8	0.3	0.5

[a]Reference 2.

gas-phase reduction enthalpies of epoxides to alcohols, by comparison to the experimental results (Table 3). In these calculations, the geometry was optimized at each level of theory studied. Table 3 also compares calculated alkene reduction enthalpies to experimental values determined using ΔH_f (g) from the literature.[2] The best computational method is then applied to additional functional groups, such as simple aziridines that are difficult to obtain in pure form, making experimental studies difficult.

In several cases, the molecules of interest have multiple low energy conformations, within 3 kcal mol^{-1} of the global minimum. The conformational profiles of these molecules were explored, and the tabulated enthalpies reflect contributions of the various conformers based on a Boltzmann distribution. The effects of including these higher-energy conformations can be significant. For example, nine conformations of 2-butanol were considered, and the weighted enthalpy is 0.36 kcal mol^{-1} greater than the global minimum, at the CBS-QB3 level of theory.

A review of the results in Table 3 suggests that G3 and CBS-APNO are the most reliable methods for modeling epoxide reductions. Similarly, G3 and CBS-APNO work best for alkene reductions. In a recent study of alkene and carbonyl reductions, Wiberg concluded that CBS-APNO, G4, and W1PW methods best reproduce experiment.[16] The energies of reactions involving H$_2$ are difficult to calculate accurately. The bond in H$_2$ is significantly different than other bond types, so defects in a computational model do not cancel out as well as when bond types in the reactants and products are more closely matched. It is thus not surprising that many of the methods agree poorly with experiment. The commonly used AM1 method is within ~5 kcal mol^{-1} on the epoxide reduction enthalpies with a mean error of 1.9 kcal mol^{-1}, but consistently over 10 kcal mol^{-1} off for the alkene reductions. The B3LYP/ 6-31G* method also does a poor job reproducing the epoxide reduction enthalpies. However, B3LYP/6-31G* performs much better on the alkene reduction enthalpies, generally within 2 kcal mol^{-1} of experimental values. Problems with the B3LYP/ 6-31G* method have recently been attributed to the way London dispersion forces and basis set superposition error are treated; the B3LYP-D3 and B3LYP-gCP-D3 methods address these issues.[17]

The relative enthalpies of the isomeric epoxides and alkenes were also considered, as shown in Table 4. More methods compare favorably to experiment: MP2/6-31G*, CBS-QB3, G2, G3, and CBS-APNO. Both density functional methods used, as well as AM1 and RHF/3-21G, still do not perform as well. Gas-phase ΔH_f are available for the thiiranes[2,3] and are also included in Table 4. These experimental data do not agree with any of the computational methods. The best computational methods found for epoxides and alkenes tend to converge on the same values for the thiiranes, suggesting that the calculations are more likely correct than the experimental data. Liebman and Greenberg have previously noted that the experimental data for thiiranes are likely to be in error.[18]

It is also of interest to compare substituent effects on other functional groups for which experimental data are not available. The G3 data are used, given the good results with this method as shown in Tables 3 and 4. Note that CBS-APNO methods cannot currently be applied to third-row atoms. Figure 1 shows the influence of substituents on the relative stabilities of epoxides, alkenes, cyclopropanes, and aziridines as determined using G3 calculations. In some of the aziridines, the NH group can be either anti or syn to the alkyl substituent(s). The inversion barrier at the aziridine nitrogen is known to be on the order of 20 kcal mol^{-1}; the stereoisomers interconvert at room temperature,[9,19] so the values tabulated reflect the energy weighted average determined by Boltzmann distribution.

In all cases, the gem-dimethyl isomer is most stable, and the relative enthalpies in Figure 1 are compared to that isomer. Substituents have the greatest influence on epoxide enthalpies, with a range of 5 kcal mol^{-1}. Substituents have less impact on the relative enthalpies of the alkenes and cyclopropanes. Figure 1 also shows the relative enthalpies of the phosphiranes and thiiranes. The barrier to invert phosphorus is significantly greater than nitrogen,[20] and results for the configurationally stable, lower energy anti structures are shown.

It has previously been observed that methyl substituents stabilize cyclopropanes; the unusually strong C−H bonds are replaced with strong C−C bonds.[21] In contrast, the stabilization of alkenes by alkyl substituents has been attributed to the electron-donating capacity of the alkyl groups, through orbital mixing of the substituent C−H bonds with the π^* orbital of the alkene.[22] We have explored whether similar hyperconjugation

Table 4. Relative Gas-Phase Enthalpies of Epoxides, Alkenes, and Thiiranes (kcal mol^{-1})

	$\Delta\Delta H_f$ (g) this study	$\Delta\Delta H_f$ (g) lit.[a]	AM1	RHF/ 3-21G	MP2/ 6-31G*	B3LYP/ 6-31G*	B3LYP/ 6-311++G**	CBS-QB3	G2	G3	CBS-APNO
				Epoxides							
cis-2,3-dimethyloxirane	1.8 ± 0.8		−0.92	1.73	1.84	0.67	0.63	1.60	1.82	1.67	1.49
trans-2,3-dimethyloxirane	0.0 ± 0.4		−1.79	−0.12	0.32	−0.78	−0.77	0.38	0.53	0.40	0.30
2,2-dimethyloxirane	0.0		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ethyloxirane	5.6 ± 0.7		−1.07	4.38	5.87	4.78	4.61	5.55	5.60	5.61	5.48
mean error, epoxides			3.7	0.5	0.2	0.9	1.0	0.2	0.2	0.2	0.2
				Alkenes							
cis-2-butene		2.40 ± 0.25	−2.09	2.31	2.71	1.79	1.81	2.64	2.91	2.70	2.57
trans-2-butene		1.27 ± 0.23	−2.08	0.64	1.07	0.34	0.48	1.42	1.54	1.39	1.36
2-methylpropene		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1-butene		4.06 ± 0.20	1.63	2.91	4.25	4.27	3.84	4.13	4.10	4.02	4.13
mean error, alkenes			3.4	0.6	0.2	0.6	0.5	0.2	0.3	0.2	0.1
mean error, epoxides and alkenes			3.6	0.5	0.2	0.7	0.8	0.2	0.2	0.2	0.2
				Thiiranes							
cis-2,3-dimethylthiirane	0.00 ± 0.71		−0.94	1.78	2.03	0.77	0.81	1.79	1.96	1.86	
trans-2,3-dimethylthiirane	−1.84 ± 0.71		−1.93	0.21	0.47	−0.70	−0.69	0.57	0.61	0.58	
2,2-dimethylthiirane	0.00		0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
ethylthiirane			−1.05	8.25	6.73	4.00	3.46	3.72	3.72	3.79	
mean error, thiiranes			0.5	1.9	2.2	1.0	1.0	2.1	2.2	2.1	

[a]Reference 2.
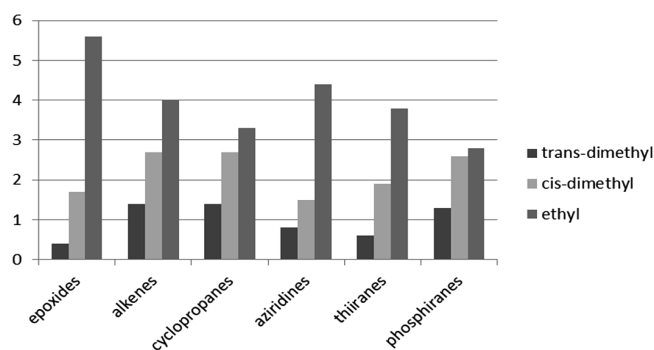
Figure 1. Relative enthalpies, compared to *gem*-dimethyl isomer, kcal mol^{-1}, G3 calculations.

Figure 2. Structural features used in Tables 5 and 6.

or bond strengths account for the differences observed for the various heterocycles, using a combination of calculated geometries and charges obtained using the Natural Population Analysis[23,24] methodology. The calculated structures and charges (Tables 5 and 6) suggest that only a weak hyperconjugation may occur if any. If hyperconjugation were to occur, one would expect alkyl substitution to cause the C−X bond to lengthen, the C2−C$_{methyl}$ bond to shorten, and the C$_{methyl}$−H bond to lengthen. Also, one would expect the charge on X to become more negative, and the charge to become more positive on the hydrogen in the alkyl substituent that is antiperiplanar with respect to the heteroatom. Figure 2 defines the relevant structural features.

In the epoxides, the C−O bond lengthens slightly from 1.437 Å in oxirane to 1.446 Å in 2,2-dimethyloxirane. The effect is small but consistent with hyperconjugation. Similarly, the charge on oxygen becomes slightly more negative with each additional alkyl substituent. However, the bond between the ring carbon and the methyl carbon is actually longer in the 2,2-dimethyloxirane compared to the other substituted compounds, but this may be due to steric crowding. The C−H bond in the methyl substituent that is antiperiplanar to the oxygen, with the
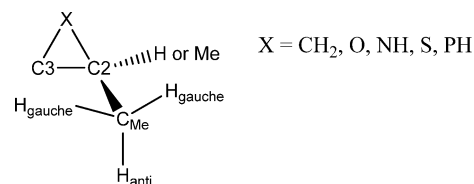
best alignment for hyperconjugation, does in fact have a slightly elongated bond, compared to the two C−H that are gauche, but again the effect is quite small, on the order of 0.001 Å. Hyperconjugation is thus not a major source of stabilization due to alkyl substitution.

The charge on the ring carbons changes significantly with alkyl substitution, going from −0.104 in oxirane to +0.086 in 2-methyloxirane, to +0.252 in 2,2-dimethyloxirane, a trend expected when the number of attached hydrogens decreases. In the case of epoxides, the destabilizing electrostatic interaction between the negative oxygen and the negative ring carbon in oxirane becomes a stabilizing interaction between the negative oxygen and a positive ring carbon with alkyl substitution. However, with this greater electrostatic stabilization, one might anticipate the C−O bond to shorten, and this is not observed. The influence of the methyl substituent on the ring carbon charge also leads to a greater electrostatic stabilization between the positively charged ring carbon and the negatively charged substituent carbon.

Similar but weaker trends are observed in the aziridines. The nitrogen does not exert as strong an inductive effect on the adjacent carbon, and the aziridine ring carbons with substituents are not as positive as in the epoxides. As such, the electrostatic stabilization of the negatively charged substituent carbon with the ring carbon is not as important a factor, but rather there is a decrease in destabilization due to two adjacent atoms with negative charge. Thus the polarization due to the oxygen and nitrogen atoms leads to stabilization between the ring carbon and both the heteroatom and the substituent carbon.

Table 5. Selected Structural Features, MP2(full)/6-31G(d) Optimization in G3 Calculation

	$r(X-C2)$, Å	$r(X-C3)$, Å	$r(C2-C3)$, Å	$r(C2-C_{Me})$, Å	$r(C_{Me}-H)$, anti to X, Å	$r(C_{Me}-H)$ gauche, Å	C-X-C, deg
oxirane	1.437		1.463				61.2
methyloxirane	1.441	1.441	1.464	1.500	1.094	1.092	61.1
						1.093	
2,2-dimethyloxirane	1.446	1.444	1.466	1.505	1.095	1.092	60.9
						1.094	
trans-2,3-dimethyloxirane	1.445		1.465	1.500	1.094	1.092	60.9
						1.093	
cis-2,3-dimethyloxirane	1.444		1.469	1.501	1.094	1.090	61.1
						1.093	
2-ethyloxirane, global min	1.443	1.441	1.464	1.501	1.097	1.095	61.0
cyclopropane	1.501		1.501				60.00
methylcyclopropane	1.502	1.505	1.502	1.507	1.094	1.095	59.9
						1.094	
gem-dimethylcyclopropane	1.503	1.508	1.503	1.509	1.096	1.094	59.9
						1.096	
aziridine	1.472		1.479				60.3
2-methylaziridine, NH *anti* to Me	1.472	1.476	1.479	1.502	1.094	1.092	60.2
						1.094	
2,2-dimethylaziridine	1.475	1.481	1.480	1.508	1.095	1.095	60.1
				1.506	1.092	1.095	
thiirane	1.814		1.479				48.1
2-methylthiirane	1.822	1.818	1.479	1.505	1.095	1.093	47.9
						1.093	
2,2-dimethylthiirane	1.831	1.821	1.479	1.510	1.096	1.092	47.0
						1.094	
phosphirane	1.866		1.488				47.0
2-methylphosphirane, PH *anti* to Me	1.873	1.870	1.486	1.509	1.095	1.094	46.8
						1.093	
2,2-dimethylphosphirane	1.879	1.875	1.487	1.511	1.097	1.094	46.7
				1.514		1.094	

The charges in the thiiranes and phosphiranes are completely different. Here, the heteroatoms are positively charged, and in the parent heterocycles, the ring carbons are even more negatively charged than in cyclopropane. In these compounds, the ionic stabilization between the heteroatom and the adjacent ring carbon actually decreases with alkyl substitution; the substituent effect thus appears to occur because the substituent carbons repel the ring carbons less.

Strain Energies. Strain energies are a useful way to compare energies of compounds that are not isomers, and they reveal the energetic cost associated with deforming a molecule away from ideal structural parameters.[25] For the compounds of interest to this study, only cyclopropane has a commonly accepted strain energy, 27.5 kcal mol^{-1}.[25] Isodesmic and related reaction types[5] are often used to determine strain energies. These hypothetical reactions are useful in computational studies because many systematic errors cancel out since the number and type of each bond is the same for the reactants and the products. Most commonly, strain energies are obtained using equations in which all but one compound is strain-free; here, the ΔH_{rxn} is the strain energy. It is also possible to use the equations when all but one compound has known strain energy. In this case, the ΔH_{rxn} is the difference in strain between reactants and products. The ΔH_{rxn} can be quite dependent on the reference compounds chosen for comparison, as recently detailed by Wheeler, Houk, Schleyer, and Allen.[5] The analysis below presents a variety of equations.

First, the strain energies of the parent epoxide and related heterocycles were determined. Two separate reactions were used, eqs 3 and 4, and giave similar results as shown in Table 7. Enthalpies calculated using the G3 method are used in the analysis as above and are compared to experiment when appropriate ΔH_f are available.[2] For molecules with more than one conformation, only the lowest energy conformer was used in the strain analysis.

The reactant heterocycles in eq 3 may have strain themselves; this strain can be determined using eq 5, where all molecules except the heterocycle are considered to be strain-free. The strain energies of the 1,4-diheterocyclohexanes were thus calculated to be 4.1 kcal mol^{-1} for X = O; 0.9 kcal mol^{-1} for X = NH; −1.7 kcal mol^{-1} for X = S; −2.1 for X = PH. These compare favorably to strain energies determined by Cox using an additivity scheme: 4.0 kcal mol^{-1} for X = O and 0.0 kcal mol^{-1} for X = NH.[26] Interestingly, the more stable conformation where X = PH has the P−H in the axial positions, with the unshared pairs of electrons in the equatorial positions.

The strain energies of oxirane and aziridine are comparable to that of cyclopropane, as has been known for quite some time. Cox reported strain energies based on additivity to be 27.5 kcal mol^{-1} for cyclopropane, ~28 kcal mol^{-1} for oxirane, and ~23 kcal mol^{-1} for aziridine.[26] Using an updated ΔH_f for aziridine,[3] its strain becomes 26.7 kcal mol^{-1}. Also using an additivity scheme, Benson found the strain in oxirane to be 26.8 kcal mol^{-1}.[27] There are several offsetting factors. The number of destabilizing torsional interactions between adjacent

Table 6. Selected NPA Atomic Charges, MP4/6-31G(2df,p), from G3 Calculation

	X	C2	C3	C_{Me}	H_{anti}	H_{gauche}	H on X
oxirane	−0.610	−0.104					
methyloxirane	−0.619	0.086	−0.098	−0.673	0.226	0.231	
						0.229	
2,2-dimethyloxirane	−0.624	0.252	−0.089	−0.658	0.224	0.228	
						0.233	
trans-2,3-dimethyloxirane	−0.629	0.092		−0.670	0.225	0.228	
						0.231	
cis-2,3-dimethyloxirane	−0.629	0.092		−0.673	0.226	0.227	
						0.232	
2-ethyloxirane, global min	−0.623	0.086	−0.093	−0.462	0.225	0.226	
cyclopropane	−0.457	−0.457					
methylcyclopropane	−0.453	−0.258	−0.453	−0.637	0.221	0.214	
						0.221	
gem-dimethylcyclopropane	−0.446	−0.083	−0.446	−0.626	0.219	0.219	
aziridine	−0.710	−0.267					0.382
2-methylaziridine, NH anti to Me	−0.716	−0.071	−0.263	−0.652	0.220	0.228	0.383
						0.224	
2,2-dimethylaziridine	−0.711	0.100	−0.255	−0.646	0.228	0.217, 0.233	0.378
				−0.639	0.218	0.224, 0.222	
thiirane	0.098	−0.543					
2-methylthiirane	0.084	−0.337	−0.530	−0.653	0.225	0.231	
						0.234	
2,2-dimethylthiirane	0.080	−0.152	−0.517	−0.641	0.222	0.236	
						0.231	
phosphirane	0.500	−0.712					−0.075
2-methylphosphirane, PH anti to Me	0.487	−0.498	−0.701	−0.643	0.222	0.221	−0.072
						0.230	
2,2-dimethylphosphirane	0.493	−0.308	−0.687	−0.631	0.219	0.226	−0.075
				−0.634		0.228	

Eq. 3

Eq. 4

Eq. 5
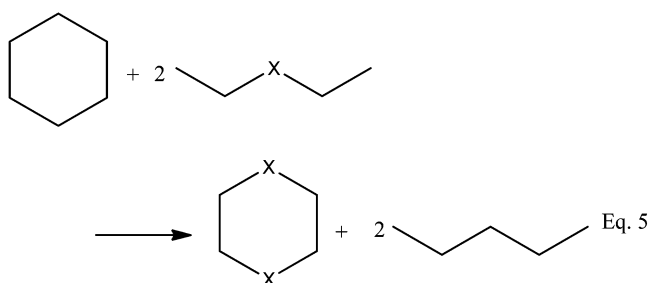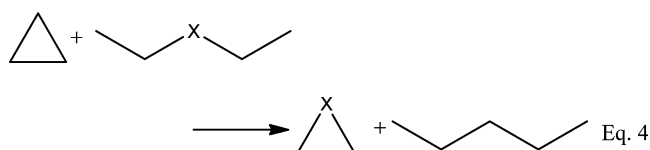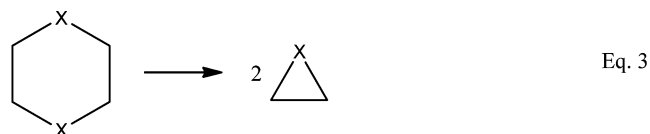
methylene groups in cyclopropane is reduced in the heterocycles. In addition, the ideal bond angle about a heteroatom is smaller than for CH_2, leading to reduced angle strain. However, the strain calculated for cyclopropane is less than one might expect due to the stabilization of the unusually strong C−H bonds;[25] there are fewer of these bonds to stabilize the heterocycles. This idea has been demonstrated by Borden in a comparison of cyclopropene and cyclopropane.[28] The low
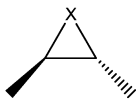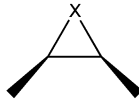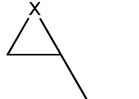
strain in thiiranes[26] and phosphirane[29] are also well established; both thiiranes and phosphiranes have longer bonds and a smaller bond angle around the heteroatom.
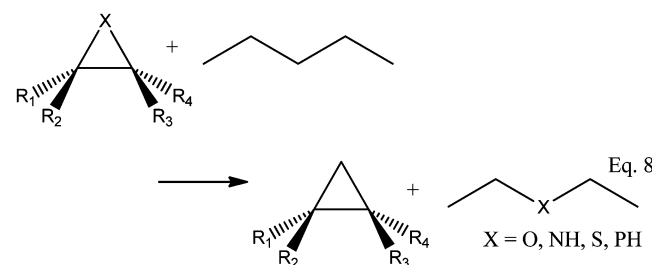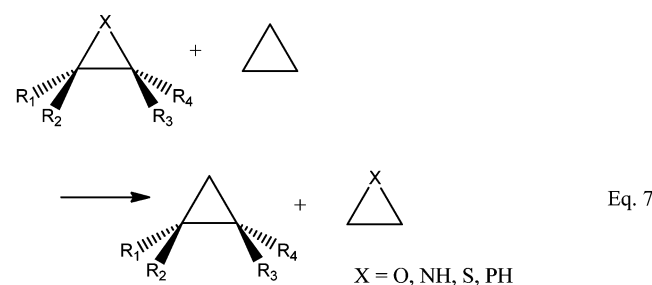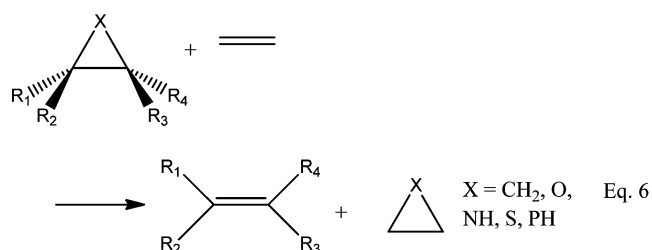
The influence of substituents on the strain energies of the various substituted compounds can also be determined using isodesmic-type reactions. First, the substituted ring compounds were compared to the corresponding substituted alkenes (eq 6). Note that ethylene is often considered strain-free, but other alkenes can experience olefinic strain that can either increase or decrease molecular strain.[25] However, the strain in the reference alkenes is small and is ignored. The strain of the parent heterocycles used in eqs 6 and 7 is the average of the values obtained in eqs 3 and 4. In eqs 7 and 8, the heterocycles are compared to cyclopropanes and require the strain energies of the substituted cyclopropanes calculated in eq 6.

Alkyl substituents on epoxides and aziridines lead to greater reduction in strain energies than cyclopropanes. As described above, this is attributed to the influence of substituents on the charge of the ring carbon. The stabilization in the thiiranes is apparent but not nearly as pronounced as in epoxides. Phosphirane strain does not appear to be influenced by alkyl substituents.
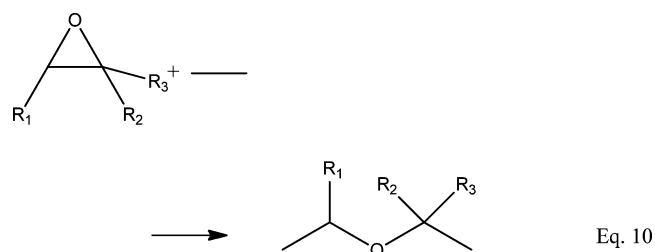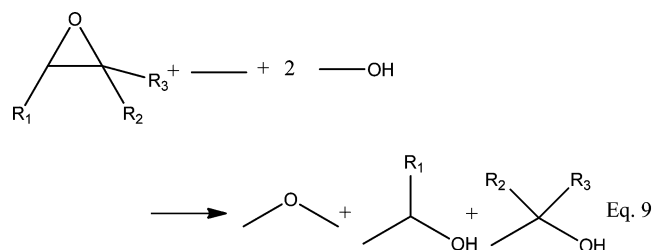
The analysis detailed above utilizes the assumption that cyclohexane is strain-free. This is not strictly true;[25] Bach has calculated the strain energy in cyclohexane to be 2.2 kcal mol^{-1} [30] using Bachrach's group equivalent approach[31] and CBS-APNO methodology. Bach has revised the strain energy in cyclopropane upward to 28.6 kcal mol^{-1}. This correction would similarly increase all of the strain energies in Table 7 by 1.1 kcal mol^{-1} but would not affect the trends.

Table 7. Strain Energies of Cyclopropanes and Heterocycles Calculated Using Eqs 3–8, G3 Calculations (kcal mol^{-1})

$X = CH_2$	Eq 3: 28.1 (27.5 expt)	Eq 6: 28.2	Eq 6: 28.2	Eq 6: 28.2	Eq 6: 27.4
$X = O$	Eq 3: 27.7 (27.3 expt)	Eq 6: 23.0	Eq 6: 22.0	Eq 6: 21.9	Eq 6: 24.4
	Eq 4: 27.1 (27.4 expt)	Eq 7: 23.0	Eq 7: 22.1	Eq 7: 22.0	Eq 7: 24.4
		Eq 8: 22.7	Eq 8: 21.7	Eq 8: 21.6	Eq 8: 24.1
$X = NH$	Eq 3: 28.0	Eq 6: 25.5	Eq 6: 24.9	Eq 6: 24.2	Eq 6: 25.6
	Eq 4: 27.5 (27.1 expt)	Eq 7: 25.6	Eq 7: 24.9	Eq 7: 24.2	Eq 7: 25.6
		Eq 8: 25.2	Eq 8: 24.6	Eq 8: 23.9	Eq 8: 25.3
$X = S$	Eq 3: 18.2	Eq 6: 16.1	Eq 6: 15.3	Eq 6: 15.2	Eq 6: 15.6
	Eq 4: 17.6	Eq 7: 16.1	Eq 7: 15.3	Eq 7: 15.2	Eq 7: 15.6
		Eq 8: 15.8	Eq 8: 15.0	Eq 8: 14.9	Eq 8: 15.3
$X = P$	Eq 3: 20.0	Eq 6: 20.5	Eq 6: 20.4	Eq 6: 20.4	Eq 6: 19.1
	Eq 4: 19.4	Eq 7: 20.5	Eq 7: 20.4	Eq 7: 20.4	Eq 7: 19.1
		Eq 8: 20.2	Eq 8: 20.1	Eq 8: 20.1	Eq 8: 18.8

Eq. 6 — X = CH$_2$, O, NH, S, PH

Eq. 7 — X = O, NH, S, PH
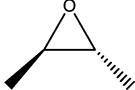
Eq. 8 — X = O, NH, S, PH

Eq. 9

Eq. 10

To avoid the potential issue with strained reference compounds, eqs 9 and 10 are proposed, where the only strained compound is the heterocycle.[32] The strain energies for oxirane and the substituted epoxides are shown in Table 8. The strain energy in oxirane is similar to that calculated in the equations above. However, the substituent effects on the epoxides are significantly smaller when using eq 9. Note that while the groups are well balanced in eq 9, the carbon–carbon bond types are not. For oxirane itself, the reactants have CH$_3$–CH$_3$

Table 8. Strain Energies of Epoxides Calculated Using Eqs 9 and 10, G3 Calculations (kcal mol⁻¹)

Eq. 9	27.8 (27.5 expt)	26.3	26.2	27.5	27.0
Eq. 10	28.1 (27.4 expt)	23.8	24.5	25.8	26.3

and CH_2−CH_2 bonds that are matched by two CH_3−CH_2 bonds in the products. This becomes a more significant mismatch in bond strengths when the epoxide is substituted. Modifications of eq 9 can be made to address this problem; however, the complexity of the reactant alkane and product alcohol(s) rapidly increases. Equation 10 also experiences the same type of differences in C−C bond types as seen in eq 9, yet the results are more similar with those obtained above. The choice of reference compounds in determining strain energies is clearly important, as has been known for some time.

Part of our motivation in undertaking this study is to understand the difference in the behavior of epoxides compared to aziridines in the presence of strong base. As noted above, the strain in oxirane and aziridine is about the same. Simple alkyl substituents decrease strain in both groups, but more so for the epoxides. We have also calculated strain energies in cyclopentene oxide and cyclohexene oxide and the corresponding aziridines, using eq 7. The strain energies of the bicycloalkanes are taken from the literature.[25] The calculated strain energies of cyclopentene oxide and cyclohexene oxide are 21.8 and 19.5 kcal mol⁻¹, respectively, while those of the corresponding aziridines are 24.3 and 22.5 kcal mol⁻¹. The higher strain in all of the aziridines and cyclopentene oxides is reflected in their propensity to undergo deprotonation at the α-position rather than β-elimination, as observed experimentally.

CONCLUSIONS

A combination of experiment and theory has been used to study the thermochemistry of epoxides and related compounds. Heats of reduction of four isomeric butene oxides are reported, and heats of formation of the epoxides in the liquid and gas phases are derived. The substituent trend in epoxides is the same as in alkenes, but epoxide relative energies vary more with substitution. Strain energies of the epoxides and related heterocycles are reported as well. The G3 and CBS-APNO computational methods best reproduce the experimental data. The computational results suggest that in epoxides bond strengthening due to greater electrostatic attractive interactions accounts for the increased stability with alkyl substitution, rather than hyperconjugation.

EXPERIMENTAL SECTION

Sample Preparation. All epoxides and alcohols used in this study are available from commercial sources and were purified by fractional distillation or preparative gas chromatography in a fume hood. The purity of the compounds used for calorimetry was >99.5% as determined by capillary gas chromatography. Samples were vacuum transferred from a drying agent ($CaSO_4$ for epoxides; 3 Å molecular sieves for alcohols) and flame-sealed under vacuum in preweighed spherical glass ampules.[33] The sample mass was determined using a microgram balance, and mass was recorded to the nearest 0.000 001 g, reproducible to ±0.000 005 g.

Reaction Calorimetry. The procedure for the calorimetry experiments has been described previously.[33] Briefly, the reaction solvent, triethylene glycol dimethyl ether, was purified by passing it through a column of freshly activated alumina under argon. Approximately 150 mL of the solvent was transferred via cannula into the oven-dried, argon-filled glass calorimetry vessel, which was already attached to the calorimeter head, and into which the sample ampule had already been placed. A commercially available 1.0 M solution of lithium triethyl borohydride in tetrahydrofuran was added by syringe (4.7 mL; 0.0047 mol, 0.5 g LiEt₃BH); this is a safer alternative than using the highly flammable solid reducing agent.

A custom reaction calorimetry system was used for the measurements. This is a largely modified Wadsö-style submarine solution calorimeter.[34,35] The airtight reaction vessel has been previously described.[36] The data acquisition system uses LabView Version 8.6 on a PC.[37] The temperature was measured using a Hewlett-Packard quartz thermometer, and the oscillations of the crystal over 10-s intervals were counted using a National Instruments 6605 counter-timer board. The oscillation frequency of the crystal is directly proportional to temperature. The oscillation count was added to a constant to give the temperature to the nearest ten-thousandth of a degree, which was logged into a datafile. The analysis of the temperature data using a FORTRAN program has been previously described.[33,35] The thermometer was calibrated against a water triple-point cell at 0 °C.

For each reaction run, an electrical calibration is also carried out. A 0.5 Ω heater made of manganin wire was powered by a National Instruments PXI-4130 power supply running at 100 mW for a set time interval, allowing the heat capacity of the system to be determined. Each reaction was repeated multiple times to obtain the uncertainty in the measurement, which is reported as twice the standard deviation from the mean, as suggested by Rossini.[38]

Ebuillometry. The boiling point of the compound (>99.5% pure) was determined at various pressures as described previously.[15] The temperature was measured using a Hewlett-Packard quartz thermometer, and the pressure was measured using a Wallace and Tiernan gauge. The data were fit to the Clausius−Clapeyron equation, which gives the ΔH_v at the midpoint of the temperature range. The procedure to correct to 298.15 K using the heat capacities of the gas and liquid was previously reported,[15] and in this study the correction amounts to 0.1−0.3 kcal mol⁻¹. The C_p's of the liquids were determined using the additivity values proposed by Chueh and Swanson.[39] The C_p's of several epoxide gases are known.[4] Gas-phase C_v's can also be obtained computationally. The B3LYP/6-31G* calculated C_v's for the four butane oxide isomers, methyl oxirane, and oxirane were scaled by 0.9613 and then converted to C_p's. In all cases, the calculated C_p's were lower than experimental values, and the calculated values were used to estimate the values for ethyloxirane and 2,2-dimethyloxirane (Table S1 in Supporting Information).

Computational Studies. Most of the calculations were carried out using Gaussian 09W.[40] The structures were optimized at each level of theory, and a frequency analysis was performed to verify that each optimized structure was a minimum on the potential energy surface. The energies were converted to enthalpies at 298 K using thermal corrections. Scale factors used are RHF/3-21G, 0.9409; MP2/6-31G*, 0.9676; B3LYP/6-31G*, 0.9894;[41] B3LYP/6-311++G**, 0.9877.[39] All other thermal corrections are unscaled. If appropriate, the conformational search option in Spartan '08[42] was used to identify other low

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energy conformational isomers. Any conformers within 3 kcal mol^{-1} of the global minimum at the RHF/3-21G level of theory were calculated at all levels of theory and were included in the calculated energies, using a Boltzman distribution of conformers. Atomic charges using the NPA method[23,24] were calculated during the G3 calculations, and the tabulated charges are from the MP4/6-31G(2df,p) portion of the calculation. The charges for oxirane were compared for each module of the G3 calculation. The charges from the MP2(full)/GTLarge calculation are significantly different than the rest and thus were not used.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Reaction calorimetry data; vapor pressure–temperature data from ebulliometry; heat capacities used in corrections to heats of vaporizations; tabulation of calculated energies and thermal energy corrections, or enthalpies; optimized geometries from G3 calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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■ REFERENCES

(1) Aziridines and Epoxides in Organic Synthesis; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006.

(2) Cox, J. D.; Pilcher, G. Thermochemistry of Organic and Organometallic Compounds; Academic Press: New York, 1970.

(3) Pedley, J. B. Thermochemical Data and Structures of Organic Compounds; Thermodynamics Research Center: College Station, TX, 1994; Vol. 1.

(4) Afeefy, H. Y.; Liebman, J. F.; Stein, S. E. In NIST Chemistry WebBook, NIST Standard Reference Database Number 69; Linstrom, P. J., Mallard, W. G., Eds.; National Institute of Standards and Technology: Gaithersburg, MD.

(5) Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. J. Am. Chem. Soc. 2009, 131, 2547.

(6) Crandall, J. K.; Apparu, M. Org. React. 1983, 29, 345.

(7) Morgan, K. M.; O'Connor, M. J.; Humphrey, J. L.; Buschman, K. E. J. Org. Chem. 2001, 66, 1600.

(8) Hodgson, D. M.; Bray, C. D. In Aziridines and Epoxides in Organic Synthesis; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006.

(9) Morgan, K. M.; Brown, G., Jr.; Pichon, M. A.; Green, G. Y. J. Phys. Org. Chem. 2011, 24, 1144.

(10) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. J. Org. Chem. 1980, 45, 1.

(11) Wiberg, K. B.; Crocker, L. S.; Morgan, K. M. J. Am. Chem. Soc. 1991, 113, 3447.

(12) Krishnamurthy, S.; Brown, H. C. J. Am. Chem. Soc. 1976, 98, 3383.

(13) Moreu, H.; Dode, M. Bull. Soc. Chim. Fr. 1937, 4, 637.

(14) Oetting, F. L. J. Phys. Chem. 1963, 67, 2757.

(15) Wiberg, K. B.; Morgan, K. M.; Maltz, H. J. Am. Chem. Soc. 1994, 116, 11067.

(16) Wiberg, K. B. J. Org. Chem. 2012, 77, 10393.

(17) Kruse, H.; Goerigk, L.; Grimme, S. J. Org. Chem. 2012, 77, 10824.

(18) Liebman, J. F.; Greenberg, A. Chem. Rev. 1989, 89, 1225.

(19) Nielsen, I. M. B. J. Phys. Chem. A 1998, 102, 3193.

(20) Carey, F. A.; Sundberg, R. J. Advanced Organic Chemistry, Part A: Structure and Mechanisms; Kluwer Academic/Plenum Publishers: New York, 2000.

(21) Bach, R. D.; Dmitrenko, O. J. Org. Chem. 2002, 67, 2588.

(22) Anslyn, E. V.; Dougherty, D. A. Modern Physical Organic Chemistry; University Science Books: Sausalito, CA, 2006.

(23) Reed, A. E.; Weinstock, R. B.; Weinhold, F. J. Chem. Phys. 1985, 83, 735.

(24) Reed, A. E.; Curtiss, L. A.; Weinhold, F. Chem. Rev. 1988, 88, 899.

(25) Wiberg, K. B. Angew. Chem., Int. Ed. Engl. 1986, 25, 312.

(26) Cox, J. D. Tetrahedron 1963, 19, 1175.

(27) Eigenmann, H. K.; Golden, D. M.; Benson, S. W. J. Phys. Chem. 1973, 77, 1687.

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

(29) Bachrach, S. M. J. Phys. Chem. 1989, 93, 7780.

(30) Bach, R. D.; Dmitrenko, O. J. Am. Chem. Soc. 2006, 128, 4598.

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

(32) We thank a reviewer for suggesting these equations.

(33) Crocker, L. S., Ph. D. Thesis, Yale University, 1989.

(34) Wiberg, K. B.; Squires, R. R. J. Chem. Thermodynam. 1979, 11, 773.

(35) Martin, E. J., Ph. D. Thesis, Yale University, 1984.

(36) Nakaji, D. Y., Ph. D. Thesis, Yale University, 1992.

(37) LabVIEW 8.6 ed.; National Instruments: Austin, TX, 2008.

(38) Rossini, F. D. In Experimental Thermochemistry; Rossini, F. D., Ed.; Interscience: New York, 1956.

(39) Andersson, M. P.; Uvdal, P. J. Phys. Chem. A 2005, 109, 2937.

(40) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09 Revision B.01; Gaussian, Inc.: Wallingford, CT, 2011.

(41) Foresman, J. B.; Frisch, A. Exploring Chemistry with Electronic Structure Methods, 2nd ed.; Gaussian, Inc.: Pittsburgh PA, 1996.

(42) Spartan '08 version 1.1.1; Wavefunction, Inc.: Irvine, CA, 2009.