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A relative approach for determining ring strain energies of heterobicyclic alkenes

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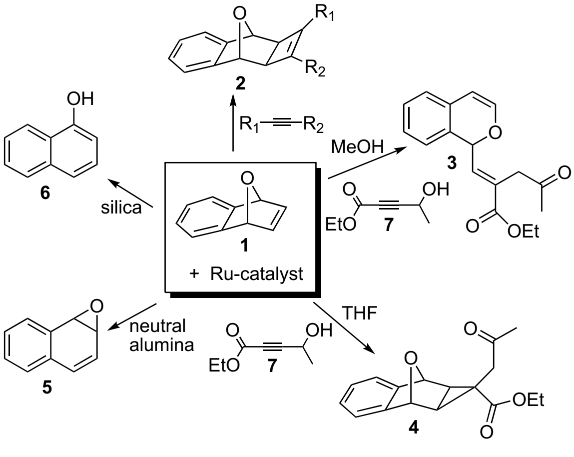
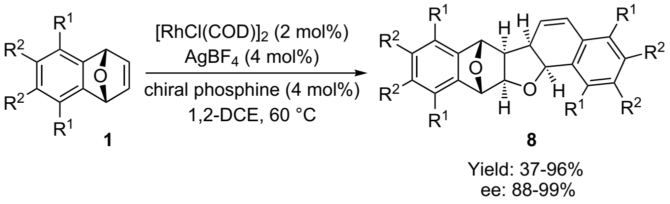
Ring strain energies (RSEs) of heterocyclic compounds are predicted compared to their analogous homocyclic compounds using the G3 method. Suitable reference compounds are devised for row 2 and row 3 heterobicyclic alkenes. Any difference in energy between the ring and the reference is due to RSE. Row 3 heterobicyclic alkene RSEs are less than those of row 2. As the electronegativity of the heteroatom increases, the RSE increases. Substitutents at the bridgehead carbons cause a decrease in RSE. [3.2.1] Heterobicyclic alkenes are significantly less strained than their [2.2.1] counterparts. Relative and absolute RSEs are reported for heterobicyclic alkenes and their derivatives.

1. Introduction

Oxabicyclic alkenes are valuable synthetic intermediates as they can serve as a general template to create highly substituted ring systems. For instance, asymmetric ring opening of these alkenes allows for the formation of several stereocenters in a single step.[1] They are also useful building blocks in molecular architecture.[2] We have recently examined different aspects of ruthenium-catalyzed reactions involving **1**, and found that depending on the reaction conditions, several products (**2**–**6**) could be obtained (Scheme 1). For example, when oxabenzonorbornadiene **1** is treated with an alkyne in the presence of the ruthenium catalyst, Cp*Ru(COD)Cl, a [2+2] cycloaddition is observed and cyclobutene cycloadduct **2** is formed.[3] When oxabenzonorbornadiene **1** is treated with the secondary propargylic alcohol **7** in the presence of the neutral Ru catalyst, Cp*Ru(COD)Cl, in MeOH or using a cationic Ru catalyst (e.g., [CpRu(CH_3CN)$_3$]PF_6), isochromene **3** is formed.[4] On the other hand, if the same reaction between **1** and **7** is carried out with Cp*Ru(COD)Cl in THF, cyclopropane **4** is produced.[5] More recently, we have observed that in the absence of an alkyne, Cp*Ru(COD)Cl catalyzes the isomerization of **1** to the corresponding naphthalene oxide **5** or naphthol **6**.[6] We have also reported that cationic rhodium(I)-catalyzed cyclodimerization of substituted oxabenzonorbornadienes produced naphtho[1,2]-furan ring systems in a single step with excellent yields and excellent enantioselectivities (Scheme 2).[7]



Scheme 1. Ru-catalyzed reactions of oxabenzonorbornadiene **1**.



Scheme 2. Rh-catalyzed asymmetric cyclodimerization of oxabenzonorbornadienes **1**.

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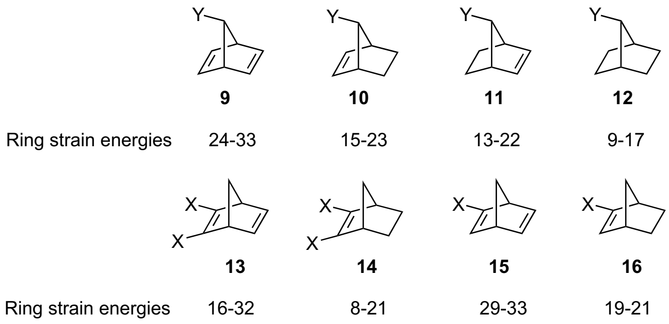
A few years ago, we investigated calculations of ring strain energy (RSE) for carbobicyclic alkenes **9**–**16** (Scheme 3).[8] The reactivities of oxabicyclic alkenes are quite different from their carbocyclic counterparts and usually oxabicyclic alkenes show a greater number of reaction pathways than carbobicyclic alkenes. One potential factor contributing to the differences in reactivity between carbobicyclic alkenes and heterobicyclic alkenes is RSE. However, virtually nothing is known about RSE for oxabicyclic alkenes and other heterobicyclic alkenes. This study intends to gain insight into the RSE of heterobicyclic alkenes compared with their carbobicyclic analogues.

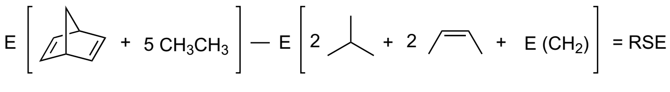


Scheme 3. Ring strain energies (kcal/mol) of carbobicyclic alkenes: Y=OAc, OTBS, O^{t}Bu, H, ^{n}hexyl, or Ph; X=COOMe, $SiMe_3$, Br, H, ^{n}hexyl or $OSiMe_3$.

The general method for the calculation of RSE is devising a reaction scheme in which the cyclic compound is a reactant, and the product is a 'broken-down' form of the cycle assumed to have no strain. The reaction equation is commonly balanced with small alkane equivalents, and the difference in energy between the reactants and products corresponds to the RSE of the cyclic compound. There are various possible forms of this method ranging from isogyric to isodesmic to hypohomodesmotic to homodesmotic to hyperhomodesmotic (in order of increasing accuracy). These differ in how well the strain free product(s) represent the bonding in the cyclic molecule. For example, isodesmic reaction schemes conserve solely the number of C–C, C=C, C–H bonds, etc. from reactants to products, whereas a hyperhomodesmotic scheme conserves bonding environment of each atom by having equivalent numbers of $H_3C–CH_2$, $H_3C–CH$, $H_3C–C$, etc. from reactants to products. The general accuracy level aspired to in the literature is homodesmotic reaction schemes for the calculation of RSE of cyclic compounds.

Recently, Wheeler et al. have clarified the definition of homodesmotic reactions equations.[9] The formal definition according to Wheeler is (a) equal numbers of each type of carbon–carbon bond (i.e., $C_{sp}–CH_{sp3}$, etc.) in the reactants and products and (b) equal numbers of each type of carbon atom (sp^3, sp^2, sp) with zero, one, two, and three hydrogens attached in reactants and products. This, clearly, would yield more accurate RSEs than an isodesmic reaction equation, which only matches formal bond types.

In our previous work, an isodesmic approach was used to calculate the ring strain energy for carbobicyclic alkenes at the 6-31G(d) B3LYP level of theory. Ring strain energy for norbornane, norbornene, and norbornadiene was calculated compared to an acyclic reference comprised of linear, strain free fragments, and equivalents of ethane were used to balance the equations (Scheme 4). The energy difference between the ring and the strainless acyclic reference corresponds to RSE. Our calculated RSE values were in reasonable agreement with Wiberg and other experimental RSEs for norbornane, norbornene, and norbornadiene (Table 1).[10] The reference compound chosen has a particularly large impact in the validity of the calculated RSEs as recently discussed by Bachrach, who exclusively uses linear all-anti compounds to comprise the strain free reference.[11]



Scheme 4. Homodesmotic equation used to calculate the ring strain energy of norbornadiene. $E(CH_2)$ is a strainless carbon equivalent and is defined as the energy difference between pentane and butane.

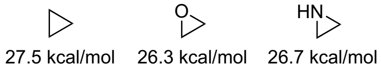
Table 1
Experimental and calculated RSEs (kcal/mol) of carbobicyclic alkenes by various methods

	Wiberg[a]	Benson[b]	6-31G(d) B3LYP[c]	G3[d]
Norbornane	14.4	—	15.5	15.1
Norbornene	19.2	27.2	20.9	18.8
Norbornadiene	—	34.7	32.8	27.6

[a] Value from Ref. 10a.
[b] Value from Ref. 10b.
[c] Calculated in our previous paper Ref. 8 (isodesmic).
[d] Calculated, this work (isodesmic).

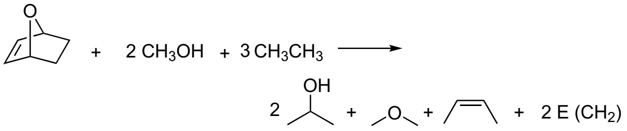
Since, the method use to calculate RSE in Scheme 4 has been reviewed due to inconsistencies with protobranching (1,3 alkyl interactions). There are many differing opinions about the impact of protobranching in organic compounds. Arguments for attractive protobranching interactions (Schleyer and Houk),[12] negative protobranching interactions (Gronert),[13] and arguments that protobranching interactions are irrelevant in calculating SE (Rogers et al.)[14] have all arisen. Scheme 4 used to calculate the RSE of norbornane, norbornene, and norbornadiene does not balance protobranching interactions on both sides of the reaction equation, although good agreement with experimental values was obtained. This paper will not delve into the protobranching argument, but that new RSE calculation methods proposed will balance protobranching interactions to avoid controversy.

Recently, Bach and Dimitrenko noted that the 6-31G(d) B3LYP method and basis set is not as accurate as the G3 method for the calculation of RSE in small rings like cyclopropane.[15] In our previous work on carbobicyclic alkenes, which had large RSEs of ~10–30 kcal/mol, variations within a few kcal/mol gave acceptable approximations for RSE. However, in simple cyclic systems, there is often only a small difference in RSE from a hydrocarbon to its analogous cyclic ether or cyclic amine (Scheme 5). Following this trend, the differences in RSE between the heterobicyclic alkenes and their parent carbobicyclic alkene may also be small. To reflect these small differences, a more precise method should be employed. In this investigation all calculations were performed with the G3 method, which has been found accurate on the order of 1 kcal/mol.[16] The RSEs of norbornane, norbornene, and norbornadiene were recalculated at this level of theory using our previous isodesmic reaction equations (Table 1) for comparison.



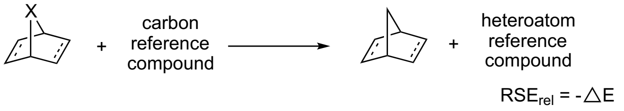
Scheme 5. Experimental ring strain energies of cyclopropane, oxirane, and aziridine.[10]

Our previously developed method for the calculation of RSE in bicyclic compounds is ill-equipped for extension to heterobicyclic molecules. When introducing heteroatoms, the acyclic reference needs to be altered to reflect the new *types* of bonds. There is no strainless equivalent for a lone heteroatom comparable to $E(CH_2)$. Thus, more molecules need to be added to the homodesmotic equation to compensate and each has its own inherent strain. It should also be noted that there is no 'formal' definition as to what constitutes homodesmoticity for non-hydrocarbons. These authors will consider homodesmoticity for hetero-molecules to mean equal numbers of each type of bond (including the hybridizations of these bonding partners) in the reactants and the products. As there are no literature values or prior calculations done on the RSE of heterobicyclic alkenes, the authors found it useful to employ isodesmic reactions (similar to those used in our prior work) as a rough basis for comparison. These reference values calculated with the modified isodesmotic reaction are denoted as RSE_{mod} (Scheme 6) are used as a reference value for validation of the new method.



Scheme 6. Modified isodesmic reaction used to calculate RSE_{mod} of oxanorbornene: $RSE = -\Delta E$.

Another approach to the calculation of heterobicyclic alkene RSE uses a relative method.[10d,17] This involves calculation of the *relative* strain of a molecule with respect to a second compound; in this case the heterocycle against the carbocycle analogue (Scheme 7). The total ring strain energy (RSE_{tot}) of the first can then be determined as the sum of the relative ring strain energy (RSE_{rel}) and the RSE of the carbocycle from literature sources if available. The relative method is by definition homodesmotic as the cyclic systems and reference compounds are closely matched in terms of bonding environments, varying in only one heteroatom. This increases the accuracy of the calculated values from our previous isodesmic reaction schemes to homodesmotic reaction schemes. This also negates problems encountered with protobranching in the previous model.



Scheme 7. Reaction used to calculate RSE_{rel} of a general heterobicyclic alkene.

The relative method suffers from the assumption that the molecules used to balance the theoretical equation are ‘strainless’. It is important that the only change in the reaction is the change in strain from a heterocycle to a carbocycle. This requires that the molecules used to balance the equation be strain free. Strain free can mean; (a) literally free of strain (hypothetical situation) or (b) the same amount of strain added to both sides of the reaction, thus canceling. This study will look for type (b) strain free references.

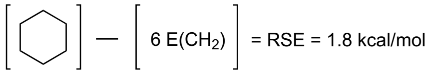
In the literature to our knowledge there is currently no simple method to quantify ring strain of heterobicyclic alkenes, which are common in organic synthetic research. We will develop appropriate strain free reference compounds to be used for the calculation of RSE_{rel} of heterobicyclic alkenes compared to their parent carbobicyclic alkenes. With this method we can gain insight into the reactivity of a heterobicyclic alkene without having an absolute RSE for the compound. We also propose to combine RSE_{rel} calculations with our previous work on RSEs of carbobicyclic alkenes where possible to quantify RSE_{tot} values for heterobicyclic alkenes.

2. Results and discussion

2.1. Choosing strainless reference compounds for the relative method of RSE calculation

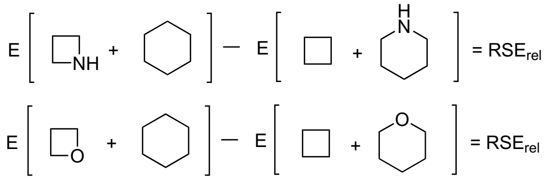
2.1.1. Simple monocyclic systems

When using the relative method to calculate RSE in simple heterocyclic systems, the choice of a reference molecule is simple. Commonly in organic chemistry the cyclohexane ring structure **17d** is thought of as having ‘negligible’ ring strain. Its oxygen and nitrogen analogues (tetrahydropyran **19d** and piperidine **18d**) have small strain as well (generally accepted as ~0 kcal/mol).[11] For computational organic chemistry the concept becomes more complex. The calculated RSE value of a six-membered ring clearly depends on the basis set, method, and reaction equation used. The RSE of cyclohexane has been looked at in depth in the literature, more recently by Bach et al. and shown to be 2.2 kcal/mol, a non-zero value.[15] It can be seen by an isodesmic model at the G3 level that the RSE of cyclohexane is 1.8 kcal/mol (Scheme 8). However, the true RSE value of cyclohexane need not be known for validation to the relative method in simple cyclic systems. The most important idea is that reference compounds be close enough in strain as to contribute equal amounts of SE on either side of the homodesmotic reaction equation.



Scheme 8. Calculation of RSE for cyclohexane using the homodesmotic method.

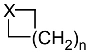
If **17d**, **18d**, and **19d** are all assumed to have RSEs of 0 kcal/mol relative to one another, they can be used as a set of strain free reference compounds to calculate the RSE_{rel} of simple heterocycles (Scheme 9). The total RSE of the nitrogen or oxygen heterocycle is the RSE_{rel} added to the RSE of the carbon homocycle (determined by the homodesmotic method). This relative method is used to calculate the RSE_{rel} and RSE_{tot} of simple heterocyclic three- to six-membered rings (Table 2) to validate its accuracy on simple systems before extension to larger heterobicyclic alkenes.



Scheme 9. Calculation of RSE_{rel} of **18b** and **19b** using strain free reference compounds.

Table 2

RSE_{rel} (kcal/mol) of heterocycles using strainless six-membered rings as reference molecules



X = CH$_2$	X = NH	X = O
17a : n = 0	**18a** : n = 0	**19a** : n = 0
17b : n = 1	**18b** : n = 1	**19b** : n = 1
17c : n = 2	**18c** : n = 2	**19c** : n = 2
17d : n = 3	**18d** : n = 3	**19d** : n = 3

Compound	RSE_{rel}	RSE_{tot}	Expt[d]
17a	N/A	28.4[a]	27.5
17b	N/A	28.9[a]	26.5
17c	N/A	7.8[a]	6.2
17d	N/A	0[b]	0.0
18a	−1.7	26.7[c]	26.3
18b	−3.5	25.4[c]	24.7
18c	−1.7	6.1[c]	5.4
18d	0.0	0[c]	0.0
19a	−1.0	27.4[c]	26.7
19b	−2.9	26.0[c]	25.2
19c	−1.0	6.8[c]	5.8
19d	0.0	0[c]	0.0

[a] Calculated directly from homodesmotic reactions.

[b] Assumption of relative method.

[c] Calculated with relative method.

[d] Literature value for RSE (Ref. 10).

The RSEs of **17** determined by isodesmic reactions are comparable to the experimental values. As previously stated, RSE for the six-membered ring reference compounds were assumed to be 0 kcal/mol with respect to one another. Overall, the relative method has been shown to give reasonable RSE values for simple heterocyclic systems.

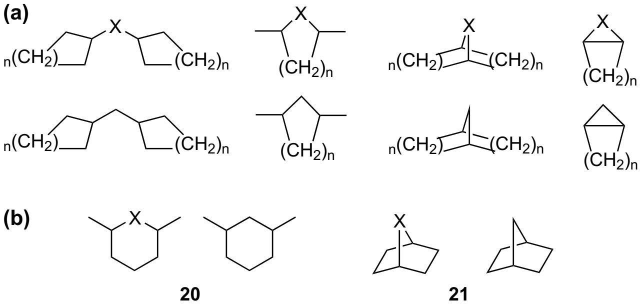
2.1.2. Heterobicyclic alkenes

The relative method can be extended to determine the RSE_{rel} of heterobicyclic alkenes. Finding a reference compound set for a bicyclic molecule is more challenging than for a monocyclic system. The bonding environment of each atom in the heterobicyclic alkene should ideally be conserved. For this to occur, the reference compounds need to have tertiary sp^3 carbons adjacent to the heteroatom (Scheme 10).

Scheme 10. Reference compound set for calculation of RSE_{rel} for heterobicyclic alkenes: X=various heteroatoms.

Initially, a reference compound where R_1=R_2=R_3=R_4=CH_3 was devised. The geometries of the carbon and oxygen derivatives optimized to give very different configurations. As the geometries were different, the inherent strains of the carbon and oxygen analogues were also very different and thus the requirements for an ideal reference molecule set were not met.

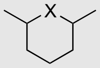
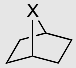
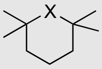
To minimize geometric differences of the potential reference compounds (to minimize the difference in strain), a conformation was imposed by the inclusion of rings. Only symmetrical reference compounds were considered. There are four possible structures for this type of molecule that satisfy the requirement of a tertiary carbon adjacent to each side of the heteroatom (Scheme 11a). These molecules were examined (n=0, 1, 2, 3, 4) and the most viable candidates were chosen by looking at the difference in RSE of the carbon, nitrogen, and oxygen analogues using the modified homodesmotic reaction. Two such structures, **20** and **21** were thought to be the closest in geometry and relative strain for the carbon and heteroatom pair (Scheme 11b).



Scheme 11. (a) Potential reference compounds for calculation of RSE_{rel} in heterobicyclic alkenes. (b) Reference compounds for calculation of RSE_{rel} of heterobicyclic alkenes.

For both reference compounds **20** and **21**, the differences in RSE of the carbon, nitrogen, and oxygen analogues were 1.1 kcal/mol or less, making either compound a reasonable reference molecule. However, reference **21** showed a smaller difference between the carbon **21a**, nitrogen **21b**, and oxygen **21c** analogues, than did reference compound **20** (Table 3). This makes reference **21** the desired compound for the calculation of RSE_{rel} for oxa- and aza-bicyclic alkenes. To use the norbornane analogues **21a**, **21b**, and **21c** as a reference compound set, their RSEs are assumed to be equal satisfying the strainless condition of the method and given the value of 15.1 kcal/mol (RSE of **21a**). This assumption neglects a difference of up to 0.6 kcal/mol (difference between **21a** and **21b**); which is considered reasonable within the limits of the G3 method.

Table 3
RSE (kcal/mol) of reference compounds used for calculation of RSE of heterobicyclic alkenes

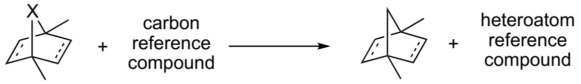
Cpd no.		Compound	X	RSE_{mod}	ΔCH_2 analogue
20	**a**		CH_2	−0.5	0
	b		NH	0.6	1.1
	c		O	0.1	0.6
	d		SiH_2	0.6	1.1
	e		PH	0.0	0.5
	f		S	−0.8	−0.3
21	**a**		CH_2	15.1	0
	b		NH	15.7	0.6
	c		O	15.4	0.3
	d		SiH_2	18.1	3.0
	e		PH	12.5	−2.6
	f		S	11.5	−3.6
22	**a**		CH_2	3.7	0
	b		NH	5.7	2.0
	c		O	4.4	0.8
23	**a**		CH_2	12.5	0
	b		NH	11.3	−1.2
	c		O	11.7	−0.9

Theoretically, the heteroatom can also be various other elements in group 14, 15 or 16. Reference compounds were formulated using silicon (**20d** and **21d**), phosphorous (**20e** and **21e**), and sulfur (**20f** and **21f**) as seen in Table 3. The smallest difference in RSE for row 3 heteroatom reference compounds compared to the carbon analogue is seen with **20** (max. 1.1 kcal/mol between **20a** and **20d**). Thus, reference **20** is the ideal compound for calculation of RSE_{rel} for row 3 heterobicyclic alkenes.

The necessity for different reference compounds for row 2 compared to row 3 heterobicyclic alkenes can be explained in part by the increased size of the heteroatom leading to different bonding environments. The electronic structures of the row 3 heteroatoms may be closer to reference compound **20** than to compound **21**.

2.1.3. Substituted heterobicyclic alkenes

Another type of heterobicyclic has substituents at the bridgehead carbons. The relative RSE method should therefore be extended to include this possibility. A simple dimethyl substituted heterobicyclic alkene was used as a model (Scheme 12). The reference molecules used for the unsubstitututed heterobicyclic alkenes **20** and **21** were adjusted such that there was a quaternary carbon on either side of the heteroatom as seen in reference compounds **22** and **23** (Table 3). Optimizations were then performed to determine the RSEs of **22** and **23** via the modified group equivalent reaction method. Reference compound **23** showed the smallest differences between the carbon (**23a**), nitrogen (**23b**), and oxygen (**23c**) analogues, making it the desired reference compound for disubstituted heterobicyclic alkenes. This requires the assumption that RSE_{rel} for **23a**, **23b**, and **23c** is negligible (acceptable condition within the limits of the G3



Scheme 12. Reaction used for the RSE_{rel} calculation of substituted heterobicyclic alkenes.

method). The RSE for these compounds was set to 12.5 kcal/mol (RSE of **23a**). Monosubstituted reference compounds were constructed, however, the RSE of the carbon, nitrogen, and oxygen analogues were different by more than 2 kcal/mol. Therefore, there was no possible strain free reference set of molecules to use in the calculation of the RSE_{rel} of monosubstituted heterobicyclic alkenes.

2.1.4. [3.2.1] Heterobicyclic alkenes

The relative method for RSE calculations also has been extended to the bicyclo[3.2.1]octane system **26**, which is also commonly seen in synthetic organic chemistry. Since **26** has the same branching around the heteroatom as in [2.2.1] bicyclic alkenes, **21** can be used as a reference to calculate RSE_{rel}.

2.2. Calculating relative ring strain

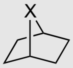
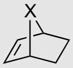
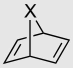
Having acquired suitable reference compounds for a variety of systems (Table 3), the RSE_{rel} of each heterobicyclic alkene compound was calculated with respect to its carbobicyclic alkene analogue (Scheme 13). The total RSE for each heterobicyclic alkene was then calculated by adding RSE_{rel} to the RSE for the carbobicyclic alkene. This value is compared with the RSE_{mod} of the heterocycle calculated directly from the modified homodesmotic method. All nitrogen norbornene derivatives are *syn* and all phosphorous norbornene derivatives are *anti* with respect to the double bond as these have been determined as the lowest energy conformations.

Scheme 13. Calculation of RSE_{rel} using Ref. 2: $\Delta E = -RSE_{rel}$.

2.2.1. Heterobicyclic alkenes

As defined, the carbon **21a**, nitrogen **21b**, and oxygen **21c** derivatives of norbornane have the same RSE. For the silicon (**21d**), phosphorous (**21e**), and sulfur (**21f**) analogues of norbornane the RSE decreases from **21d** to **21e** to **21f** (Table 4). For the norbornene (**24**) and norbornadiene (**25**) derivatives in Table 4, it can be seen that as the heteroatom increases in electronegativity from carbon to nitrogen to oxygen the RSE of the heterobicyclic alkene increases. When the heteroatom is a row 3 element, the RSE of the heterobicyclic alkene decreases compared to its row 2 counterpart. This is in part due to the increased carbon–heteroatom bond length from row 2 to row 3 allowing for closer to ideal bond angles at the heteroatom bridge. Similarly, going from silicon to phosphorous to sulfur, the RSE of the heterobicyclic alkene generally increases as the electronegativity increases. As the heteroatom changes to a more electronegative element, it withdraws electron density from anti-bonding π-orbitals, which is reflected in the decrease in bond length of the carbon–carbon double bonds (Fig. 1). As anti-bonding character is reduced, the bond strength increases, the ring size decreases and as a result the RSE of the heterobicyclic alkene increases. These trends indicate that the electronegativity of the heteroatom is a primary factor in determining RSE. Both RSE_{rel} and RSE_{mod} yield comparable values, indicating the validity of the RSE_{rel} method.

Table 4
RSEs (kcal/mol) of heterobicyclic alkenes using relative method

Cpd no.		Cmpd	X	Ref Cpd	RSE_{rel}	RSE_{tot}	RSE_{mod}
21	**a**	 X	CH_2		0	15.1	15.1
	b		NH	**21**	0	15.1	15.1
	c		O		0	15.1	15.1
	d		SiH_2		1.8	17.0	18.1
	e		PH	**20**	−3.1	12.0	12.5
	f		S		−3.4	11.8	11.5
24	**a**	 X	CH_2		0	18.8	18.8
	b		NH (*syn*)	**21**	1.1	19.8	20.4
	c		O		3.1	21.9	22.1
	d		SiH_2		−3.3	15.5	16.6
	e		PH (*anti*)	**20**	−4.8	13.9	14.4
	f		S		−0.3	18.5	18.3
25	**a**	 X	CH_2		0	27.6	27.6
	b		NH	**21**	5.4	33.0	33.6
	c		O		8.2	35.8	36.1
	d		SiH_2		−13.0	14.6	15.8
	e		PH	**20**	−6.9	20.8	21.3
	f		S		3.3	30.9	30.7

2.2.2. [3.2.1] Heterobicyclic alkenes

The [3.2.1] bicyclic alkenes **26** and **27** are significantly less strained than their [2.2.1] counterparts due to the increased bridge size. A larger bridge allows for ideal bond angles, relieving strain in the molecule. This shows that increasing or decreasing the size of a bridge has a great effect on the RSE of a heterobicyclic alkene. However, the same general trend is followed in which the RSE increases from carbon to *syn* nitrogen to oxygen (Table 5). Compound **27** containing a double bond has higher RSE than **26** without a double bond. Both the relative method and using the modified homodesmotic reactions yield similar RSEs.

2.2.3. Substituted heterobicyclic alkenes

In general the disubstituted heterobicyclic compounds **23**, **28**, and **29** are less strained than the unsubstituted compounds **21**, **24**, and **25**, but the order of ring strain follows the same trend (Table 5). The carbon analogue is less strained than the nitrogen analogue, which is less strained than the oxygen analogue. The methyl substituents at the bridgehead carbons have steric interactions with the bicyclic alkene, allowing for a larger bond angle at the heteroatom. This relieves strain in the heterobicyclic alkene compared to the unsubstituted bicyclic alkene (Table 6), explaining the decrease in strain energy. The difference in RSE between the unsubstituted and disubstituted heterobicyclic alkene is small, ranging from 1.8 to 2.9 kcal/mol (Tables 4 and 5), indicating that substituents at the bridgehead carbons do not have a large impact on the RSE of a heterobicyclic alkene.

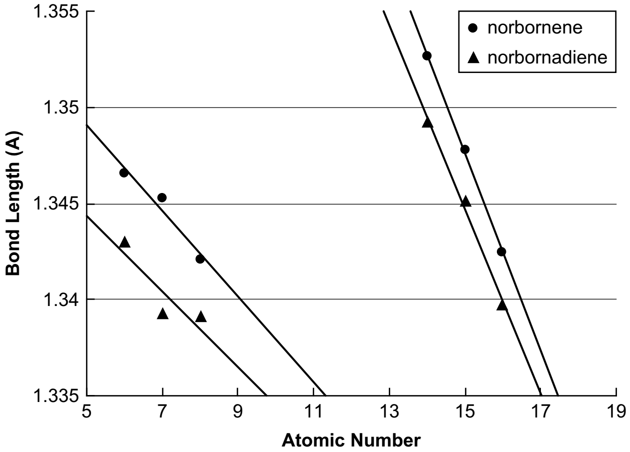
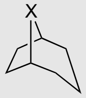
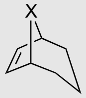


Figure 1. The length of the carbon–carbon double bond in heterocyclic alkenes based on the heteroatom.

Table 5
RSE (kcal/mol) of substituted and [3.2.1]heterobicyclic alkenes using relative method

Cpd no.		Cmpd	X	Ref. Cmpd	RSE_{rel}	RSE_{tot}	RSE_{mod}
26	**a**		CH_2	**21**	0	9.3	9.3
	b		NH (*syn*)		−0.3	9.0	9.6
	c		O		−0.4	8.9	9.2
27	**a**		CH_2		0	11.2	11.2
	b		NH (*syn*)		0.7	11.9	12.5
	c		O		1.9	13.1	13.4
23	**a**		CH_2	**23**	0	12.5	12.5
	b		NH		0	12.5	11.7
	c		O		0	12.5	11.3
28	**a**		CH_2		0	16.3	16.3
	b		NH (*syn*)		0.8	17.2	16.3
	c		O		2.7	19.0	17.8
29	**a**		CH_2		0	25.8	25.8
	b		NH		4.9	30.7	29.8
	c		O		7.4	33.2	32.0

2.2.4. Benzo-heterobicyclic alkenes

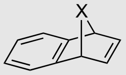
The benzonorbornadiene system **30** is another common heterobicyclic alkene derivative. It would be virtually impossible to create a homodesmotic reaction equation to represent the RSE of this system. However, the RSE_{rel} of heterobenzonorbornadiene systems can be calculated with the relative approach using reference **20** and **21** for the appropriate heteroatoms (Table 7). The hetero-benzonorbornadienes follow the same trend as seen for the other heterobicyclic alkenes; as the electronegativity of the heteroatom increases, the RSE of the benzonorbornadiene increases. No absolute RSE is known for these compounds, however, it may be inferred solely based on RSE that oxabenzonorbornadiene **30c** would be more reactive than aza (**30b**) or carbo (**30a**) benzonorbornadiene due to its higher RSE (dependent on the type of reaction involved). It can also be seen that the phosphorous analogue **30d** has a negative RSE_{rel} indicating that it would likely be more stable than the carbobenzonorbornadiene as it possesses less strain. It was not possible to optimize the silicon derivative of benzonorbornadiene using the G3 method. Information about the RSE_{rel} of a silicon derivative could possibly be obtained using a less rigorous calculation method.

The relative method is ideal for any hetero-compounds in which there would be difficulty constructing a strain free reference compound to use the modified homodesmotic method. Although in these cases an absolute RSE cannot be determined, the RSE_{rel} on its own can provide insight into the differences in reactivity of the hetero- and hydrocarbon analogues. This is seen in the case of benzonorbornadiene and derivatives.

Table 6
Angle formed at heteroatom in unsubstituted and disubstituted heterobicyclic alkenes

Angle of heteroatom bridge (°)				
Unsubstituted		Disubstituted		Difference
21a	94.5	**28a**	95.9	1.4
24a	93.9	**29a**	95.2	1.4
25a	92.4	**30a**	93.7	1.3
21b	95.1	**28b**	96.5	1.4
24b	94.5	**29b**	95.8	1.3
25b	92.9	**30b**	94.2	1.2
21c	96.0	**28c**	97.3	1.3
24c	95.6	**29c**	96.8	1.2
25c	94.4	**30c**	95.6	1.2

Table 7
Relative RSE (kcal/mol) of heterobenzonorbornadienes

Compound			X	Reference Cmpd	RSE_{rel}
30	**a**		CH_2	N/A	0
	b		NH (*syn*)	**21**	5.2
	c		O		8.4
	d		PH (*anti*)	**20**	−7.5
	e		S		1.6

anti and *syn* are with respect to the carbon–carbon double bond.

3. Conclusions

The relative approach to RSEs has been extended by developing appropriate reference molecules for heterobicyclic systems. These reference systems can be used to determine the relative ring strain of a heterobicyclic alkene with respect to the carbobicyclic alkene analogue. The RSE_{tot} of the heterobicyclic system may be determined if the RSE of the carbobicyclic alkene is known. The sum of the RSE of the carbobicyclic compound and the RSE_{rel} of the heterobicyclic alkene is RSE_{tot} of the heterobicyclic alkene.

The validity of a reference compound can be confirmed based on its relative strain compared with the carbon analogue using a modified homodesmotic approach. It has been noted that row 2 heterocycles require a norbornane analogue as a reference compound compared with row 3 heterocycles, which use a disubstituted six-membered ring structure as a reference compound. This difference is partially due to the change in bonding environment of the larger heteroatoms.

This is the first study to quantify RSE in heterobicyclic alkenes. Relative RSEs provide insight to the broad reactivity of oxabicyclic alkenes compared with their corresponding carbobicyclic alkenes. More electronegative heteroatoms yield higher RSE for the heterobicyclic alkenes due to shorter carbon–heteroatom bonds and stronger carbon–carbon double bonds. Substituted heterobicyclic alkenes show smaller RSE due to the larger bond angle at the heteroatom bridge. [3.2.1] Bicyclic systems have significantly decreased RSE compared to their [2.2.1] Bicyclic counterparts.

This study indicates that the relative method of RSE calculation at the G3 level of theory can be used to predict RSEs in heterocyclic molecules comparable to those derived solely from a homodesmotic method. The relative method of calculation is especially important in instances where a modified homodesmotic method cannot be used.

4. Computational methods

All predictions were made with Gaussian03.[18] The G3 method was used to determine all RSEs, and is generally considered accurate to about 1 kcal/mol. All geometries were optimized and structures had no imaginary vibrational frequencies indicating minimum energy forms. In the case of two possible conformations, the lower energy structure was evaluated.

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Supplementary data

Total energies, Cartesian coordinates, and reactions used to calculate RSEs for structures **20** to **30** follow this paper in the web version of this journal. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.090.

References and notes

1. (a) For selected examples, see: Lautens, M.; Fagnou, K.; Heibert, S. *Acc. Chem. Res.* **2003**, *36*, 48; (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834; (c) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437; (d) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884; (e) Wu, M. S.; Jeganmohan, M.; Cheng, C. H. *J. Org. Chem.* **2005**, *70*, 9545; (f) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373; (g) Zhang, W.; Wang, L. X.; Shi, W. J.; Zhou, Q. L. *J. Org. Chem.* **2005**, *70*, 3734; (h) Cabrera, S.; Arrayás, R. G.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938; (i) Li, M.; Yan, X. X.; Zhu, X. Z.; Cao, B. X.; Sun, J.; Hou, X. L. *Org. Lett.* **2004**, *6*, 2833 and references therein.
2. For selected examples of molecular architecture, see: (a) Girreser, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Philp, D.; Stoddart, J. F. *Pure Appl. Chem.* **1993**, *65*, 119; (b) Warrener, R. N.; Margetic, D.; Sun, G.; Amarasekara, A. S.; Foley, P.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1999**, *40*, 4111; (c) Warrener, R. N.; Butler, D. N.; Margetic, D.; Pfeffer, F. M.; Russell, R. A. *Tetrahedron Lett.* **2000**, *41*, 4671; (d) Warrener, R. N. *Eur. J. Org. Chem.* **2000**, 3363; (e) Warrener, R. N.; Margetic, D.; Foley, P.; Butler, D. N.; Winling, A.; Beales, K. A.; Russell, R. A. *Tetrahedron* **2001**, *57*, 571; (f) Dalphond, J.; Bazzi, H. S.; Kahrim, K.; Sleiman, H. F. *Macromol. Chem. Phys.* **2002**, *203*, 1988; (g) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879.
3. For our recent studies of Ru-catalyzed [2+2] cycloadditions of bicyclic alkenes and alkynes, see: (a) Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031; (b) Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367; (c) Jordan, R. W.; Tam, W. *Tetrahedron Lett.* **2002**, *43*, 6051; (d) Villeneuve, K.; Jordan, R. W.; Tam, W. *Synlett* **2003**, 2123; (e) Villeneuve, K.; Tam, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 610; (f) Villeneuve, K.; Riddell, N. G.; Jordan, R. W.; Tsui, G.; Tam, W. *Org. Lett.* **2004**, *6*, 4543; (g) Jordan, R. W.; Khoury, P. R.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2004**, *69*, 8467; (h) Riddell, N. G.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681; (i) Riddell, N. G.; Tam, W. *J. Org. Chem.* **2006**, *71*, 1943; (j) Liu, P.; Jordan, R. W.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2006**, *71*, 3793; (k) Jordan, R. W.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2006**, *71*, 5830; (l) Allen, A.; Villeneuve, K.; Cockburn, N.; Fatila, E.; Riddell, N.; Tam, W. *Eur. J. Org. Chem.* **2008**, 4178.
4. (a) Villeneuve, K.; Tam, W. *Eur. J. Org. Chem.* **2006**, 5499; (b) Villeneuve, K.; Tam, W. *Organometallics* **2007**, *26*, 6082.
5. Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843.
6. Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, *128*, 3514.
7. Allen, A.; Le Marquand, P.; Burton, R.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2007**, *72*, 7849.
8. Khoury, P. R.; Goddard, J. D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103.
9. Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 2547.
10. Experimental RSE values come from: (a) Wiberg, K. B. *Agnew. Chem., Int. Ed. Engl.* **1986**, *25*, 312; (b) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279; (c) Eigenmann, H. K.; Golden, D. M.; Benson, S. W. *J. Phys. Chem.* **1973**, 77–1687; (d) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 4450 and references therein.
11. Bachrach, S. M. *J. Org. Chem.* **2008**, *73*, 2466.
12. Wodrich, M. D.; Wannere, C. S.; Mo, Y,; Jarowski, P. D.; Houk, K. N.; Schleyer, P. v. R. *Chem.—Eur. J.* **2007**, *13*, 7731.
13. Gronert, S. *J. Org. Chem.* **2006**, *71*, 1209.
14. Zavitsas, A. A.; Matsunaga, N.; Rogers, D. W. *J. Phys. Chem. A* **2008**, *112*, 5734.
15. While G3 gives a RSE of 27.55 kcal/mol, B3LYP 6-31G(d) gives 29.05 kcal/mol, nearly 2 kcal/mol different from the accepted RSE value of 27.5 kcal/mol Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2006**, *128*, 4598.
16. Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764 the overall average absolute deviation from experiment for 299 test cases was 1.02 kcal/mol.
17. (a) For examples of using a relative method for the calculation of RSE see: Rodriquez, C. F.; Williams, I. H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 953. See also Ref. 10(d).
18. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; 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.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.