Bridgehead Olefins

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Do Anti-Bredt Natural Products Exist? Olefin Strain Energy as a Predictor of Isolability**

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In memory of Paul von Ragué Schleyer

Abstract: *Bredt's rule holds a special place in the realm of physical organic chemistry, but its application to natural products chemistry—the field in which the rule was originally formulated—is not well defined. Herein, the use of olefin strain (OS) energy as a readily calculated predictor of the stability of natural products containing a bridgehead alkene is introduced. Schleyer first used OS energies to classify parent bridgehead alkenes into "isolable", "observable", and "unstable" classes. OS calculations on natural products, using contemporary forcefield methods, unequivocally predict all structurally verified bridgehead alkene natural products to be "isolable". Thus, when one assigns the structure of a putative bridgehead alkene natural product, an OS in the "observable" or "unstable" ranges is a red flag for error.*

In the early 1900s Julius Bredt developed the concept of his namesake rule,[1] which was founded on observations made in the field of monoterpene structure determination.[1,2] Bredt's rule states that "the terminus of a double bond cannot exist at the bridgehead position of a caged bicyclic system" (i.e. bicyclo[m.n.o]-**1**, Figure 1).[3] The physical origin of Bredt's rule is the high degree of strain brought about by inclusion of an *E*-alkene into a small ring.[4] Extensive fundamental investigations have tested the limits of applicability of Bredt's rule and produced various empirical measures, such as S and τ values (Figure 1) with which to understand the relative stabilities of different bridgehead alkenes.[3,5]

However, the relevance of these studies, which focused on small synthetic parent systems, to the stabilities of complex natural products (NPs) is unclear.[6] Conceivably, dense functionality that is often associated with NPs might allow an otherwise unstable framework to become isolable. However, there are no simple guidelines to aid NP chemists in determining whether a bridgehead alkene represents a viable structure for a newly discovered NP.[7,8] This problem is reflected in a number of literature reports that have proposed NP structures in obvious violation of Bredt's rule.[9] In several of these cases, subsequent recognition of the anti-Bredt character led to structural reassignment.[10] In order to provide clarity to this situation, we sought a new criterion that could be used to determine whether a putative anti-Bredt NP structure would be capable of isolation.

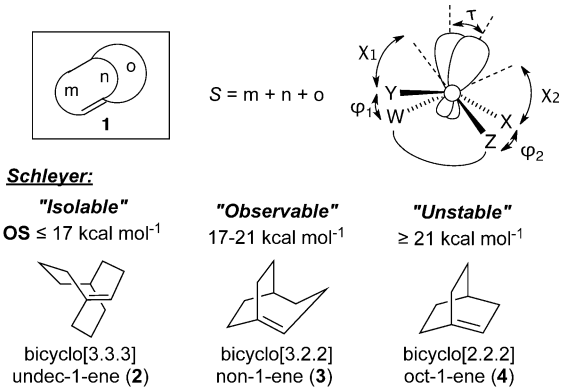

Figure 1. Top: Generalized structure of a bicyclo[m.n.o] system containing a bridgehead double bond (**1**); Fawcett's S value formula; and projected view along a torsionally distorted olefin WXC=CYZ, used to derive the value of τ, which can be determined from the average of the torsional angles WC1C2Y (ϕ_1) or XC1C2Z (ϕ_2) [that is, $\tau = (\phi_1 + \phi_2)/2$]. Taken from Refs. [5, 7]. Bottom: Schleyer's classification of bridgehead alkenes (olefins) as "isolable", "observable", or "unstable" based on olefin strain (OS) energy.

In the early 1980s, Schleyer described a forcefield-based method for predicting the stabilities of bridgehead alkenes.[11] He computed the olefin strain (OS) energies of 54 bridgehead alkenes with MM1 (OS energy being defined as the difference between the total strain energy of the alkene and that of the corresponding alkane). A correlation between the alkenes' OS energies and their experimentally observed behavior enabled the alkenes to be classified into three groups: "isolable" ($\mathrm{OS} \leq 17\ \mathrm{kcal\,mol^{-1}}$), for example **2**; "observable" ($17 \leq \mathrm{OS} \leq 21\ \mathrm{kcal\,mol^{-1}}$), for example **3**; and "unstable" ($\mathrm{OS} \geq 21\ \mathrm{kcal\,mol^{-1}}$), for example **4** (Figure 1).[11–14] The OS energies of several alkenes that were unknown at the time were calculated and their stabilities predicted; several of these predictions were later experimentally verified.[15]

Herein, we demonstrate that OS energies provide a useful tool for NP structure determination. OS energies calculated

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with contemporary forcefields offer a simple diagnostic test of the likely stability of a putative bridgehead alkene NP.

The development of an OS-based classification protocol for NPs first required determination of the OS energy ranges corresponding to isolable/observable/unstable alkenes using contemporary forcefield calculations. For this purpose we employed a series of 25 bicyclic cage alkenes, taken from Schleyer's original set, representing the full spectrum of OS ranges (i.e. high, medium, low, and negative). Energy minimization of the alkenes and their corresponding alkanes with the MM2, MM3, and OPLS-AA forcefields, as implemented in Tinker 7.1,[16] and with the MM3*, MMFF, OPLS, and OPLS_2005 forcefields as implemented in MacroModel 10.6,[17] led to a series of OS energies and notional cutoff ranges for each forcefield (Figure 2).

The stabilities of alkenes lying at the extreme ends of the OS spectrum (i.e. the very most and the very least stable) are reliably predicted by all of the forcefields, even allowing for the inevitable scatter in the most highly strained alkenes. The transitions from "isolable" to "observable" and from "observable" to "unstable" character cannot be pinpointed precisely. Rather than defining specific cutoffs between the classes, we suggest that the OS energies instead be regarded as a gauge of the reliability of structural assignments for putative bridgehead alkene NPs. Thus, if the OS energy of a proposed bridgehead alkene falls anywhere other than firmly within the "isolable" range, then the proposed structure should be treated with caution. An OS energy within the "unstable" range would be an obvious red flag for revision of the structure, while an OS energy within the "observable" range (or a few kcal mol^{-1} below) would raise doubts concerning the accuracy of the proposed structure.

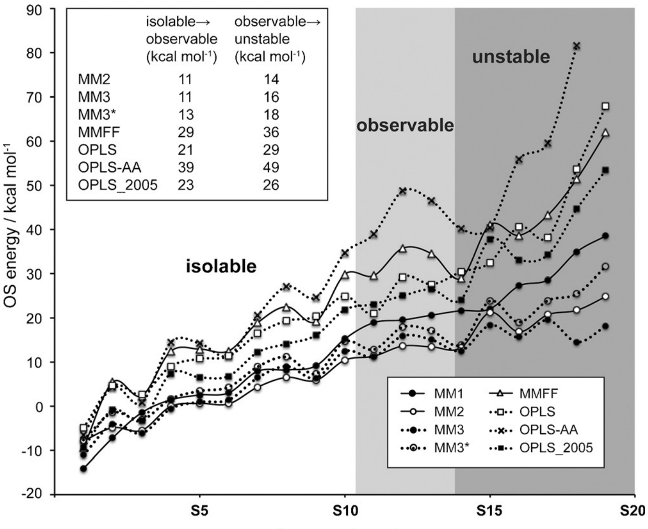
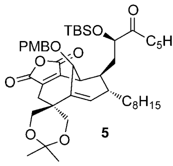
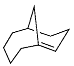
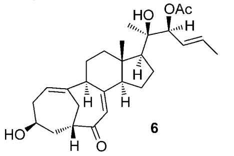
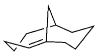
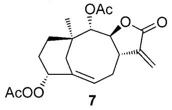
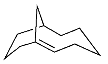
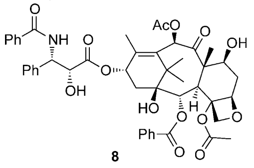
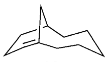
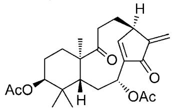
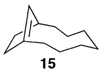
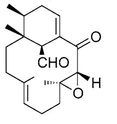
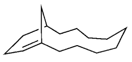


Figure 2. Olefin strain (OS) energies [kcal mol^{-1}] for a set of bicyclic bridgehead cage alkenes computed with different forcefields. The alkenes are ordered by compound number; structures are given in the Supporting Information. The top inset lists the OS ranges associated with the transitions from isolable to observable and from observable to unstable alkene character for each forcefield.

Using these criteria, the stabilities of the currently known bridgehead alkene NPs (or close analogues) for which X-ray crystallographic data are available (**5**–**10**, Table 1), were predicted. Table 1 summarizes results obtained with OPLS_2005 calculations, which can be considered representative. Table 1 also lists the OS energies of the parent bicyclic skeleton of each NP (**11**–**16**). Energies calculated with other forcefields are provided in the Supporting Information. A clear trend is evident: all of the crystallographically verified bridgehead alkene NPs fall unequivocally into the "isolable" category. The OS energies range from −9 to 2 kcal mol^{-1}, well below the isolable/observable cutoff (ca. 23 kcal mol^{-1}). Each of the parent alkenes is also predicted to be isolable. This

Table 1: Calculated OS energies of bridgehead alkene NPs (or advanced synthetic intermediates) and the corresponding parent hydrocarbons.

Entry Bicyclo-[m.n.o][a]	NP olefin distortion τ[b]	Natural product OS, prediction[c]	Parent alkene OS, prediction[c]
1 [4.3.1][18]	8.2°	 **5** 2.3,[d] isolable	 **11** 6.8, isolable
2 [4.4.1][19]	2.6°	 **6** −8.1, isolable	 **12** −3.2, isolable
3 [5.3.1][20]	3.4°	 **7** −6.9, isolable	 **13** −3.7, isolable
4 [5.3.1][21]	3.6°	 **8** −9.0, isolable	 **14** 0.5, isolable
5 [7.2.1][22]	2.6°	 **9** −8.6, isolable	 **15** −10.0, isolable
6 [9.3.1][23]	0.4°	 **10** −3.1, isolable	 **16** −5.3, isolable

[a] Literature X-ray data references. [b] Bridgehead olefin distortion (τ) values taken from X-ray data.[7] [c] OPLS_2005 OS values are shown [kcal mol^{-1}]. [d] Compound **5** is an advanced synthetic intermediate towards the [4.3.1]bicyclic phomoidrides. No NP in the [4.3.1] series has been crystallographically characterized. The C_8H_{15} group of **5** was modeled as Me, C_5H_9 as Me, PMB as Me, and TBS as TMS.

indicates that the stabilities of NPs **5**–**10** are an inherent property of the bicyclic framework. In some cases, the NP's stability is enhanced by the substituents, while in other cases the NP is a few kcal mol^{-1} less stable than the hydrocarbon core, but in no case are functional groups alone responsible for converting an observable or unstable anti-Bredt skeleton into an isolable alkene.

In NPs **5**–**10**, the degree of olefin distortion measured by the torsional angle τ (defined in Figure 1) correlates inversely with ring size. However, there is no correlation between olefin distortion and OS energy. This reflects the fact that OS is determined not only by olefin distortion, but also by the strain within the σ framework of the bicyclic system and by interactions among the substituents.

We applied the OS diagnostic to a number of putative bridgehead alkene NPs from the literature whose structures have not yet been crystallographically determined (Figure 3). The nudicaulin aglycon, whose structure was first proposed to be **17**,[9c] was recently reassigned as **18** by Schneider and Bringmann.[10b] The extremely high OS energy of **17** (77 kcal mol^{-1}) supports the rationale for reassignment. Similarly, we recently suggested[10a] that the anti-Bredt structure originally proposed[9d] for neoveratrenone (**19**) should be reformulated as **20**. OS calculations predict that **19** would not be isolable, giving support to the reassignment. The OS of the novel bridgehead alkene NP EBC-219 (**21**) falls firmly in the isolable range, supporting our original assignment[6b] for this compound, which was based on NMR spectroscopy. Conversely, three other NPs from the literature (**22**–**24**) have been proposed[6c,9a,b] to have anti-Bredt structures, but the computed OS values predict these compounds to be unstable. Reassignment of the structures of these compounds therefore appears to be in order.

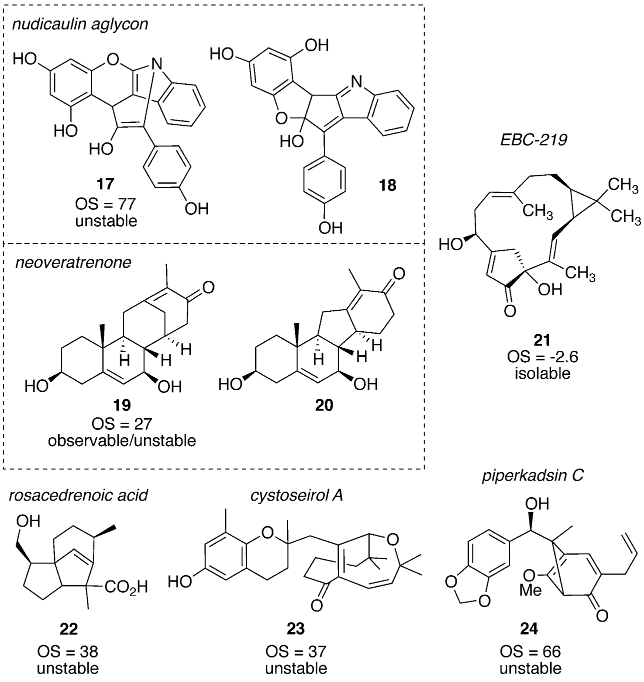


Figure 3. OS-based stability predictions for putative bridgehead alkene NPs [kcal mol^{-1}].

We used density functional theory (DFT) calculations to verify the accuracy of the forcefield-based alkene stability predictions.[24] Reoptimization of the geometries with M06-2X/6-31G(d), followed by single-point energy calculations on both the DFT-optimized and forcefield-optimized geometries with M06-2X/Def2-TZVPP, gave an estimate of the degree of alkene strain not captured by the forcefield calculation. In this way, the DFT "corrections" obtained for **7**, **10**, **19**, and **21** were small, lying between −2 and +2 kcal mol^{-1}. For **22**, the DFT correction was larger (−8 kcal mol^{-1}), but confirmed the forcefield-based prediction that **22** is unstable.

While OS energy therefore appears to be a useful and simple diagnostic tool, the behavior of a NP depends not only on its thermodynamic stability but also on its kinetic stability under the conditions used for extraction, isolation, and storage. Three NPs that contain reactive bridgehead double bonds are known: cerorubenic acid-I (**25**),[25] FR182877 (**26**),[26,27] and sesquiterpene **27**[28,29] (Figure 4). Both **25** and **26** undergo slow aerial oxidation to give epoxides (e.g. **28**). Sesquiterpene **27** was co-isolated with Michael adduct **29** (believed to be an artifact of isolation) and also forms an adduct with methanol (**30**). Initially we speculated that these reactions might indicate that **25**–**27** are "observable" rather than "isolable" bridgehead alkenes[7] (albeit towards the longer-lived end of the observable range[13]). However, the OS energies of **25**–**27** (Figure 4) all fall within the "isolable" range, suggesting that their reactivity may be promoted through kinetic rather than thermodynamic effects. DFT calculations confirm this idea, predicting that the transition state for addition of OH$^-$ to **27** is about 2 kcal mol^{-1} lower in

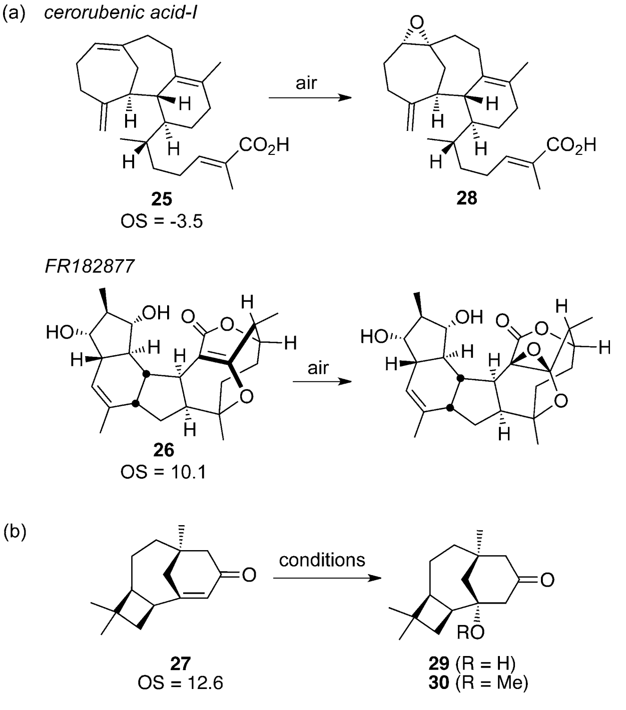


Figure 4. Known examples of NPs containing a reactive bridgehead double bond: a) cerorubenic acid-I (**25**) and FR182877 (**26**) undergo epoxidation in air; b) sesquiterpene **27** undergoes Michael addition of water or methanol.

energy than the transition state for addition to a model "unstrained" enone, cyclohexenone (see the Supporting Information).

In conclusion, although Bredt's rule has long captivated physical organic chemists,[30] the application of Bredt's rule in the context of natural products chemistry has not previously been investigated on a quantitative basis. We have shown that olefin strain (OS)-based stability predictions, first developed by Schleyer for hydrocarbons, are applicable to complex NPs. All known NPs that contain bridgehead double bonds have OS energies that predict "isolable" character. Thus, calculation of OS energy, which may be straightforwardly accomplished using forcefield methods, is recommended as a viability test for any new NP that is proposed to contain a bridgehead double bond. Even the most reactive bridgehead alkenes obtained from natural sources (**25**–**27**) are "isolable" according to the OS criterion. For this reason, we conclude that there are no anti-Bredt NPs. Bredt himself recognized that his rule may not stand the test of time, as larger-ring bridgehead alkenes were already starting to appear.[31] Of course, there exists the possibility that NPs containing latent anti-Bredt functionality will be isolated in the future and the stabilities of such molecules can be evaluated using the OS ranges reported herein.

Keywords: anti-Bredt · Bredt's rule · bridgehead olefins · natural products · strained molecules

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