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Lancifodilactone G: Insights about an Unusually Stable Enol

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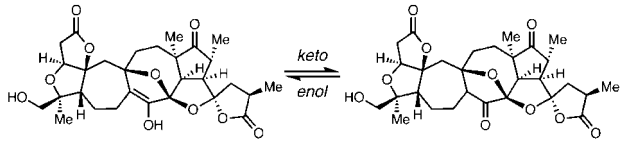

From quantum mechanics calculations we confirm that the naturally occurring enol lancifodilactone G is stable over the keto form (by 2.6 kcal/mol in water), the only known stable aliphatic enol (devoid of conjugated or bulky aromatics and lacking a 1,3-diketone structural motif known to stabilize enols). We determine architectural elements responsible for the enol stabilization and find a mechanism for keto−enol conversion in solution. In addition, we correct previously reported computational results that were performed on the misinterpreted structure demonstrating that the enol form of this natural product is more stable than previously thought.

As far back as 1880 Erlenmeyer postulated the existence of enols as thermodynamically unstable transient intermediates.[1] Studies of the simplest enol, ethenol, have revealed the thermodynamic instability relative to acetaldehyde to be 8.5 kcal/mol experimentally and 14.9 kcal/mol with computational methods.[2] It has been proposed that the theoretical value is actually closer to the real value due to errors in the indirect thermochemical methods used to measure the equilibrium constant.[2] Enols have recently been identified as common intermediates in the oxidation of hydrocarbons, after eluding the flame chemistry community for almost 150 years, and the current combustion mechanisms are under revision.[3] The kinetic barriers to keto−enol tautomerism in ethenol tend to be quite large in the gas phase with calculated energies ranging from 75 to 162 kcal/mol depending on the level of theory and mechanism of interconversion.[2] Acid and base catalysis have been shown to substantially lower the kinetic barrier with acid catalysis exhibiting the most profound effect on the barrier.[2]

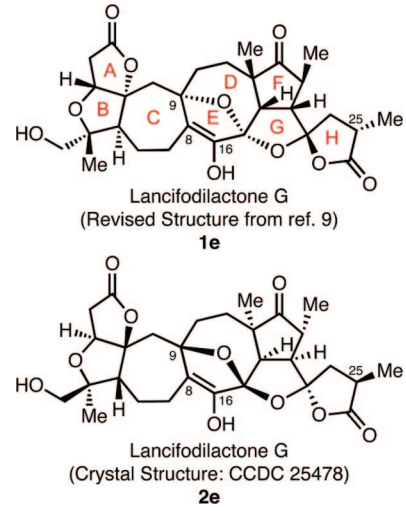

FIGURE 1. **2e** is the structure of lancifodilactone G based on the crystal structure coordinates (CCDC 25478) from ref 7. Note that the figure with the structure of lancifodilactone G (**2e**) in ref 7 incorrectly shows an epimer at C25. This was corrected to **1e** in ref 9, which assigns the absolute stereochemistry based on biogenetic extrapolation.

From a simple analysis of bond dissociation energies (BDE), one expects the ketone to be more thermodynamically stable than the enol. The C=C bond dissociation energy of ethylene is worth 174.1 kcal/mol while the C=O bond dissociation energy of formaldehyde is worth 178.8 kcal/mol, a difference of 4.7 kcal/mol favoring the stability of the carbonyl bond.[4,5] While this is purely an estimate of the origins of keto versus enol stability, it does provide some insight. When considering the tautomerism of simple aliphatic ketones, the thermodynamic stability of the ketone is often favored by 10−14 kcal/mol over the enol tautomer.[2]

Even though ketones are often generalized as being more thermodynamically stable than their enol counterparts, this is not always the case. There have been several reports of thermodynamically stable enols but most derive their stability from conjugation of the enol double bond.[6] Nonresonance stabilized enols are less common and owe their intriguing stability to steric and geometric constraints.[2,4] The discovery of enols in nature has been relatively rare with only a few natural products containing this presumably unstable functionality.[2,6,7]

Lancifodilactone G (Figure 1) is an intriguing natural product containing a stable aliphatic enol within the core of its structure (carbon 8 and 16) and exhibiting modest anti-HIV activity.[7,8] Lancifodilactone G was originally reported as the epimer of structure **2e** at carbon 25; however, the structure was recently

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(8) Carbon numbering is assigned according to the parent natural product in ref 5.

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revised,[9,10] to compound **1e**, which reflects the correct C25 epimer and an absolute stereochemistry based on a biogenetic proposal extrapolated from micrandilactone B.[11] Although structural revision has been made the originally reported computational predictions regarding the natural products thermodynamic stability relative to its ketone tautomer as well as the tautomerization mechanism have not been corrected to reflect the actual structure of the natural product.

Several questions arise when considering a stable enol such as lancifodilactone G including thermodynamic versus kinetic stability. It is possible for the enol structure to persist when in fact it is thermodynamically unstable if the activation energy to tautomerization is sufficiently large. If the structural properties giving rise to a stable enol such as lancifodilactone G can be elucidated, the design of a new class of stable enols may be realized. Stable enols could have potentially important applications as new molecular recognition scaffolds, drug discovery platforms, or molecular switches. The ability of a stable enol to shuttle between two well-defined tautomeric states by an external stimulus such as photoactivation would be particularly interesting due to the interconversion between a hydrogen bond donor and hydrogen bond acceptor mode in addition to geometrical changes. Using computational methods to evaluate the thermodynamic and kinetic energies of lancifodilactone G is a first step to understanding the stability of the enol that lies at the core of its structure.

Our goal was to elucidate the thermodynamic stability of the keto versus enol forms of lancifodilactone G and to evaluate the previously proposed kinetic barrier for the tautomerization. In addition, we sought to gain insight into the major architectural features endowing this unique stable aliphatic enol with its unparalleled thermodynamic stability. All calculations were performed by using the B3LYP hybrid DFT functional[12] with the 6-311G** basis set[13] as implemented in the Jaguar 6.5 software package[14] on the most stable conformers of lancifodilactone G. All stationary points have been identified as local minima (zero imaginary frequencies) or transition states (TS) (one imaginary frequency). Vibrational frequencies have been calculated at all stationary points to obtain zero point energies (ZPE) and free energies. In addition to electronic energy and thermodynamic contributions, we considered single-point solvent effects for H_2O (probe radius = 1.40 Å, ϵ = 80.37) using the Jaguar self-consistent Poisson−Boltzmann solver.[15]

First, we investigated the relative thermodynamic stabilities of the tautomeric forms of lancifodilactone G using the coordinates obtained from the crystal structure reported by Xiao et al.[7] We found that the keto and enol form were almost equally stable with an energetic difference of ΔE = 0.6 kcal/mol (ΔG = 0.5 kcal/mol) for the less stable enol relative to the keto form in the gas phase (Figure 2) This is in contrast to previous results which showed that enol isomers were less stable by at least 4.4 kcal/mol; however, we determined these calculations were performed on the incorrectly reported epimer of lancifodilactone G.[7] The small difference that we find in thermodynamic stability between the keto and enol form could easily be shifted in either direction by solvent effects or pH.

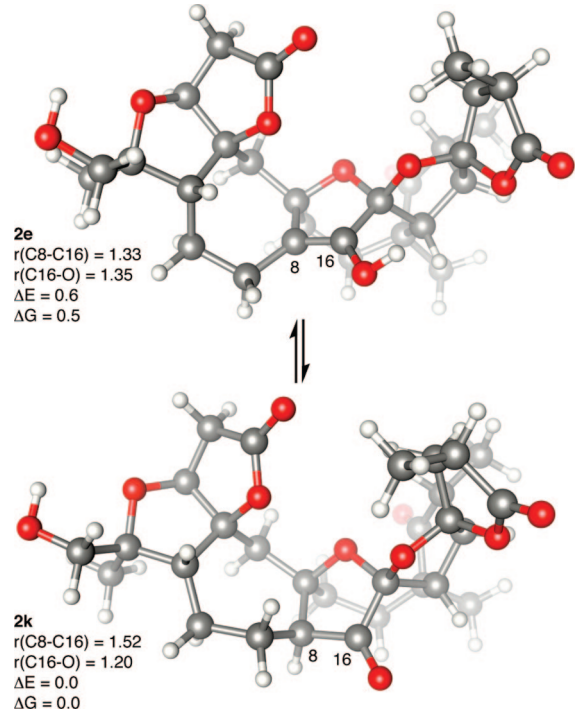

FIGURE 2. Keto and enol forms of Lancifodilactone G. Bond distances are provided in angstroms. To our knowledge, this represents the most stable aliphatic enol natural product to date.

In an effort to elucidate the architectural features primarily responsible for the stability of the enol in lancifodilactone G, we performed DFT calculations on keto and enol forms of compounds **3**−**8** (Figure 3). As shown in Figure 3, simple aliphatic enols such as **3e** tend to be thermodynamically disfavored (ΔE_{enol} = 15 kcal/mol) relative to their keto counterparts. Tetrasubstitution of enols lowers this thermodynamic difference (**4e**, ΔE_{enol} = 11.5 kcal/mol) and incorporation of the enol into an 8-membered ring as found in lancifodilactone G increases the stability of the enol (**5e**, ΔE_{enol} = 9.9 kcal/mol). Fusion of the G-ring of the natural product, **6e**, has the most dramatic stabilizing effect on the enol (ΔE_{enol} = 3.1 kcal/mol). Further addition of the F-ring (**7e**) was found to have a minor (0.1 kcal/mol) impact on enol stability, while addition of the C- and E-ring (**8e**) was found to have a slight destabilizing effect (ΔE_{enol} = 4.7 kcal/mol). Interestingly when one moves from **8e** to the natural product (**2e**) there is a large increase in the stabilization of the enol with respect to the keto form resulting in the near isoenergetic keto−enol ground states for lancifodilactone G. The overall architectural features responsible for the unusual stability of this aliphatic enol can be summed up as the combination of tetrasubstitution (3.5 kcal/mol), 8-membered-ring constraint (2.6 kcal/mol), optimal rigidification of the cyclooctane ring (C, F, G 5.2 kcal/mol), and trannsannualar effects in addition to further constraints from the A-, B-, and H-rings favoring the enol form of the natural product (4.1

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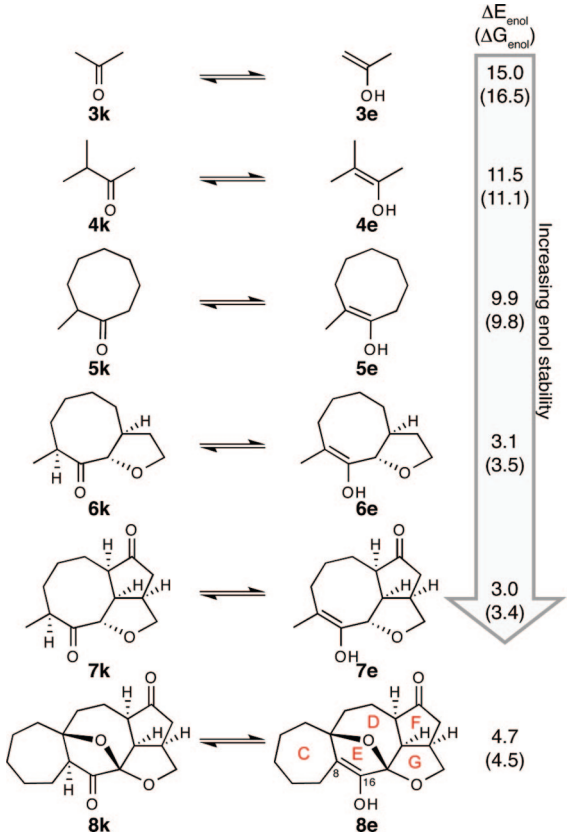

FIGURE 3. Lancifodilactone G architectural features contributing to enhanced thermodynamic enol stability. Relative stabilities (in kcal/mol) of the enol are with respect to the keto form.

kcal/mol). In principle, these concepts of enol stabilization could be used for the design of novel enol architectures.

After establishing thermodynamic stabilities, we investigated the previously proposed concerted 1,3-hydrogen shift enolization mechanism of Xiao et al.[7] We calculated the kinetic barriers for concerted tautomerization via 1,3-hydrogen shift, monowater-catalyzed, and diwater-catalyzed reaction pathways to evaluate the feasibility of a concerted mechanism. We anticipated that only one of the two possible ketone isomers could form in the enolization process as shown in Figure 2 based on protonation from the bottom face versus the sterically hindered top face. In addition, we expected the barrier for the 1−3 hydrogen shift pathway would be relatively high and unlikely to occur in an aqueous environment. We found the activation barrier for the 1,3-hydrogen shift pathway (**2-TS**, Figure 4) to be 75.7 kcal/mol ($\Delta G^{\ddagger}$ = 73.8 kcal/mol), precluding this mechanism as a plausible enolization pathway for lancifodilactone G. This is consistent with a previously proposed 1,3-hydrogen shift pathway on the incorrect epimeric form resulting in a barrier of 74 kcal/mol.[7] This is an orbital symmetry disallowed process explaining the inordinately high barrier.[2]

In addition, we calculated the concerted processes in which one or two waters catalyze enolization. We found a significant decrease in activation energy compared to the 1,3-hydrogen shift pathway. The monowater-catalyzed reaction (**2-TS-H2O**, Figure 4) has a barrier of 41.3 kcal/mol ($\Delta G^{\ddagger}$ = 43.2 kcal/mol), which is 34.4 kcal/mol ($\Delta\Delta G^{\ddagger}$ = 30.6 kcal/mol) lower than that of the 1,3-hydrogen shift pathway. The diwater catalyzed enolization barrier (**2-TS-2H2O**, Figure 4) was found to be 38.1 kcal/mol ($\Delta G^{\ddagger}$ = 37.1 kcal/mol), which is slightly lower than the monowater-catalyzed barrier by 3.2 kcal/mol ($\Delta\Delta G^{\ddagger}$ = 6.1 kcal/mol).

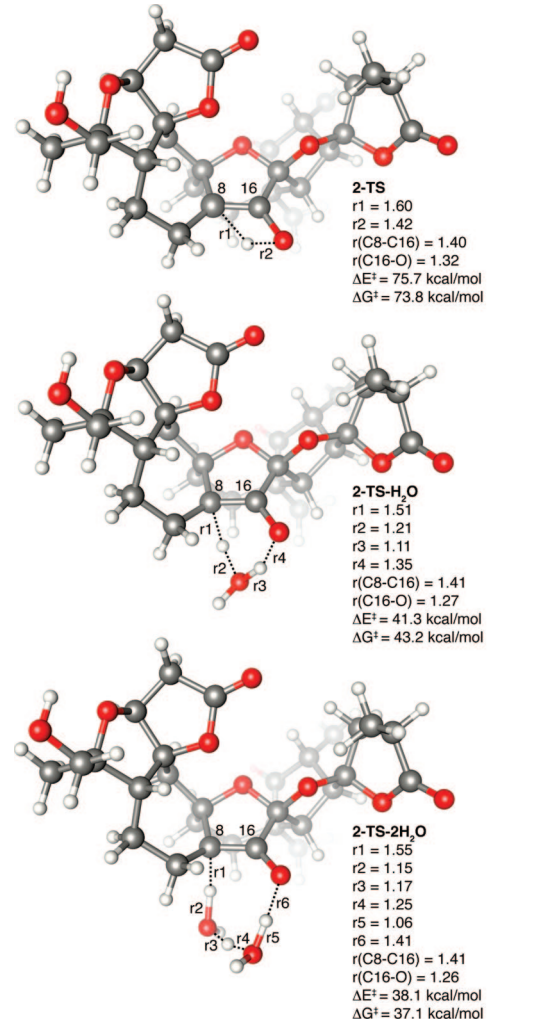

FIGURE 4. Transition state structures for keto−enol tautomerization via 1,3-hydrogen shift and mono- and diwater catalysis. Bond distances are provided in angstroms.

Next, we investigated solvent effects on the energetics of the monowater-catalyzed process and found that the enol (**2e**) is more stable than the keto form (**2k**) by ΔE = 2.6 kcal/mol in water. Absence of the explicit water molecule results in near isoenergetic keto−enol tautomers with a difference of 0.2 kcal/mol in favor of the keto form. This demonstrates the importance of explicit solvent effects to properly account for donor/acceptor properties. In addition, we found that the activation barrier decreased to $\Delta E^{\ddagger}$ = 37.8 kcal/mol. These results are in agreement with recent ab initio molecular dynamics studies on the tautomerization of acetone where up to 28 explicit water molecules were used to evaluate the kinetic barrier, which was determined to be 38.5 kcal/mol.[16] For bulk solvent we expect the contribution from explicit solvent molecules to have an even more profound effect on the enolization energetics. While the concerted mono- and diwater enolization pathways demonstrate a pronounced decrease in barrier height, they are still prohibitively high and do not accurately reflect experimental enolization

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rates (barriers have been shown to be as low as ~10−20 kcal/mol)[17] demonstrating that the conventional stepwise mechanisms is likely to dominate. In addition, acid and base catalysis has been shown to have a substantial effect on the kinetic barriers to enolization/ketonization.[17] Experimental studies have indicated that the uncatalyzed ketonization of several enols occurs by a stepwise mechanism rather than a concerted cyclic route.[18] Kinetic studies of the tautomerization of lancifodilactone G under acid/base-catalyzed conditions would provide valuable insight into this unusually stable enol; however, it may prove to be unstable under these conditions resulting in β elimination of the oxygen across the C8−C9 bond with concomitant opening of the G- and H-rings. Interestingly NMR characterization was conducted in pyridine after the original isolation showing only the enol form.[7]

In contrast to previous studies, we have demonstrated that the keto and enol forms of lancifodilactone G are nearly isoenergetic. Small differences in energy are observed in the gas phase, which favors the keto, whereas the presence of an explicit water in a dielectric continuum favors the enol, and this is consistent with previous theoretical studies on keto−enol tautomerization involving simple carbonyl derivates.[19] In addition, we find that stabilization of the enol is dramatically influenced by a combination of structural features including tetrasubstitution around the double bond, geometrical constraint imposed by an 8-membered ring, and a juxtaposition of geometrical and transannular effects from additional functionality in the natural product. The barrier to the disallowed suprafacial 1,3-hydrogen shift enolization mechanism was found to be prohibitively high ($\Delta E^{\ddagger} = 75.7$ kcal/mol). The concerted water-catalyzed processes dramatically reduce the enolization barrier by as much as $\Delta\Delta E^{\ddagger} = 37$ kcal/mol; however, the barrier is still quite high illustrating the need for consideration of conventional stepwise mechanims along with acid- and base-catalyzed processes to accurately describe the kinetics of tautomerization processes.

The absolute stereochemistry of lancifodilactone G still remains to be proven by total synthesis; however, efforts are being made in this direction.[20] It is our hope that this theoretical investigation will prompt experimental studies on the keto−enol stability of this unique natural product. Physical studies could be conducted to probe the equilibrium constants for keto−enol tautomerization, using NMR, flash photolysis, or other techniques in a range of solvents elucidating the energetics of this intriguing stable natural enol.

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Supporting Information Available: Absolute energies and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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