Alkaloids

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Mechanism of the Vinylcyclobutane Rearrangement of Sceptrin to Ageliferin and Nagelamide E**

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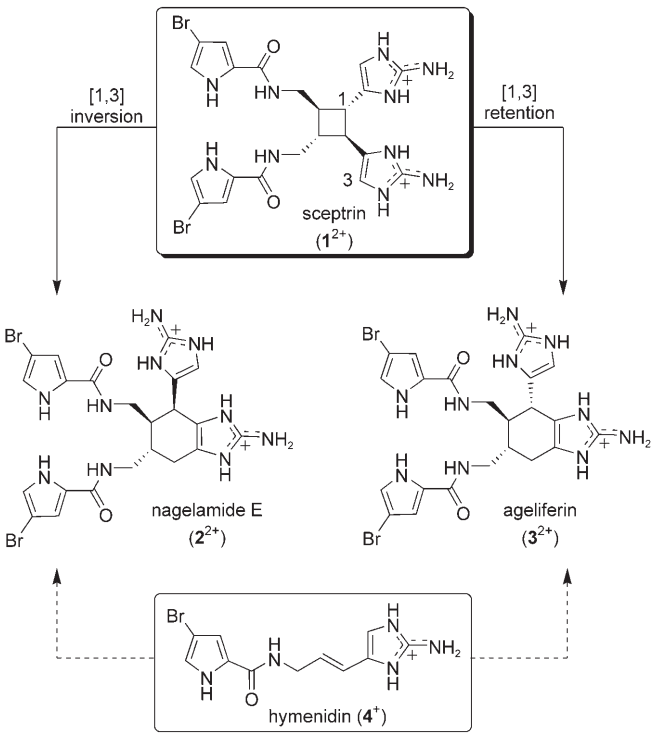
Chemical transformations that have been the focus of extensive physical organic studies are sometimes later discovered to be operative in natural processes. The Bergman cyclization of (*Z*)-3-ene-1,5-diynes, for example, was explored mechanistically and found to involve *p*-benzyne diradical intermediates.[1] A little over a decade later, it was discovered that the Bergman cyclization was a critical component of the biological activity of a newly discovered class of enediyne natural antibiotics that have potent antitumor activity.[2]

We now provide theoretical evidence that the well-studied vinylcyclobutane–cyclohexene rearrangement, which involves a 1,4-diradical "*para* intermediate",[3] is involved not only in a synthetic but also a biosynthetic process. The recent synthesis[4] of the antiviral compound ageliferin ($\mathbf{3}^{2+}$)[5] from sceptrin ($\mathbf{1}^{2+}$)[6] led to the proposed involvement of a vinylcyclobutane–cyclohexene rearrangement[7] (Scheme 1). Therefore, a reaction previously of interest for mechanistic reasons is likely to be an important step in a biosynthesis.

Dimeric pyrrole–imidazole alkaloids[8] are believed to be derived from hymenidin ($\mathbf{4}^{+}$)[4] and related structures (see Scheme 1). The reigning biosynthetic hypothesis[4,9] is that nagelamide E ($\mathbf{2}^{2+}$) and $\mathbf{3}^{2+}$ are likely formed from two equivalents of $\mathbf{4}^{+}$ through an enzymatic "Diels–Alderase",



Scheme 1. Solid arrows: The vinylcyclobutane rearrangements of $\mathbf{1}^{2+}$ to $\mathbf{2}^{2+}$ and $\mathbf{3}^{2+}$. Atoms that become bonded in the [1,3] shift are labeled 1 and 3 on $\mathbf{1}^{2+}$. Dashed arrows: $\mathbf{4}^{+}$ as a possible precursor to complex pyrrole–imidazole alkaloids $\mathbf{2}^{2+}$ and $\mathbf{3}^{2+}$ by an enzymatic "Diels–Alderase".

but recent results[4] suggest the involvement of the vinylcyclobutane–cyclohexene rearrangement of $\mathbf{1}^{2+}$ to $\mathbf{2}^{2+}$. Such rearrangements are alternatives to the previous biosynthetic hypothesis for the formation of $\mathbf{2}^{2+}$ and $\mathbf{3}^{2+}$. Subsequent to our initial report on the synthesis of $\mathbf{3}^{2+}$,[4] preparation of the natural product in larger quantities led to the isolation of small quantities of a compound tentatively assigned as an epimer of $\mathbf{3}^{2+}$. This compound was later reported as the natural product $\mathbf{2}^{2+}$,[10] which was isolated by Kobayashi and co-workers from an unidentified *Agelas* marine sponge along with $\mathbf{3}^{2+}$ in a ratio of 1:24. Herein, we report the first total synthesis of $\mathbf{2}^{2+}$ and computational studies that have led to a clear understanding of the mechanism and stereoselectivity of this remarkable rearrangement.

Microwave irradiation of $\mathbf{1}^{2+}$ in water at 200 °C for 5 minutes followed by purification by reversed-phase HPLC gave a 40% yield of $\mathbf{3}^{2+}$, 50% recovery of $\mathbf{1}^{2+}$,[4] and a small amount of $\mathbf{2}^{2+}$. Although the amount of isolated $\mathbf{2}^{2+}$ varied somewhat and the small quantities of material involved made precise measurements difficult, the yield was consistently around 2% (ca. 1:20 ratio with $\mathbf{3}^{2+}$). Microwave heating of pure $\mathbf{3}^{2+}$ at 200 °C was found to generate a mixture of $\mathbf{3}^{2+}$ and $\mathbf{2}^{2+}$. A final concentration of 2:1 was reached after 7 minutes, and further heating led only to decomposition. This result suggests either that $\mathbf{1}^{2+}$ could be the direct biosynthetic precursor to both $\mathbf{3}^{2+}$ and $\mathbf{2}^{2+}$ or that $\mathbf{1}^{2+}$ could be an indirect precursor through the epimerization of $\mathbf{3}^{2+}$. Given the small amounts of $\mathbf{2}^{2+}$ isolated relative to $\mathbf{3}^{2+}$, it is also possible that

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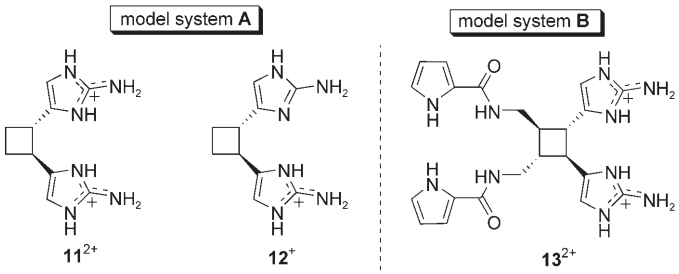
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

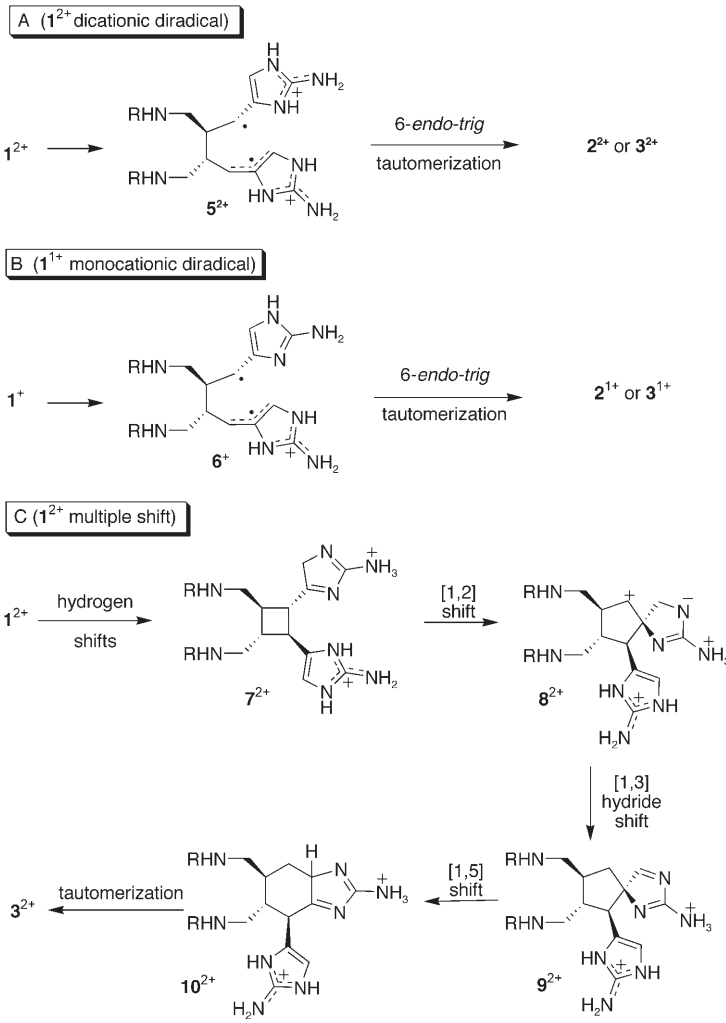
$\mathbf{2}^{2+}$ is an artifact produced from $\mathbf{3}^{2+}$ during isolation rather than a compound produced in nature. The isolation of $\mathbf{2}^{2+}$ was significant, as it involves inversion of the imidazole-bearing stereocenter, as opposed to the retention of configuration in the formation of $\mathbf{3}^{2+}$.

Experimental[7,11] and theoretical[12] investigations show that the rearrangements of substituted vinylcyclobutanes to cyclohexenes proceed via diradicals, although no distinct intermediates are present on the potential-energy surface. Simple vinylcyclobutanes rearrange to give a mixture of all four stereochemical outcomes (suprafacial or antarafacial with inversion or retention, hereafter referred to as: si, sr, ai, and ar) and often show a slight preference for symmetry-allowed products si and ar.[7,11–12] However, subtle stereochemical changes in the starting vinylcyclobutane may invert this preference and lead to the symmetry forbidden products sr and ai.[7,11] The rearrangements of $\mathbf{1}^{2+}$ to $\mathbf{3}^{2+}$ and $\mathbf{2}^{2+}$ could occur by three possible mechanisms.[4,13] Vinylcyclobutane rearrangement via a dicationic diradical ($\mathbf{1}^{2+}$; Scheme 2A) or a monocationic diradical ($\mathbf{1}^{1+}$; Scheme 2B), followed by tautomerization, are both possible. In addition, a dicationic multiple-shift mechanism with $\mathbf{1}^{2+}$ (Scheme 2C) that involves a 1,2 and a 1,5 shift combined with several tautomerizations could occur. While retention or inversion of configuration at the migrating carbon atom can unambiguously be observed in the product stereochemistries, $\mathbf{3}^{2+}$ and $\mathbf{2}^{2+}$ lack the stereochemical indicators necessary to determine whether the rearrangement proceeds suprafacially or antarafacially.

Computational studies of the rearrangements of $\mathbf{1}^{2+}$ were performed on the two model systems shown in Scheme 3.



Scheme 3. Simplified model compounds used in the computational study of the rearrangements of $\mathbf{1}^{2+}$.



Scheme 2. A)–C) Three potential mechanisms for the rearrangement of $\mathbf{12}^{+}$ to nagelamide E ($\mathbf{2}^{2+}$) and ageliferin ($\mathbf{3}^{2+}$) that have been studied computationally.

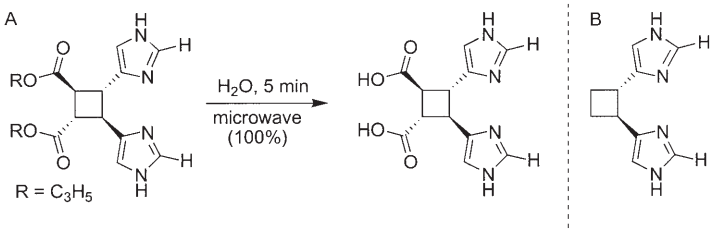
Model system A ($\mathbf{11}^{2+}$ and $\mathbf{12}^{+}$) lacks the neutral side chains of $\mathbf{12}^{+}$, whereas model system B ($\mathbf{12}^{2+}$) includes the side chains but replaces both pyrrole bromine atoms with hydrogen atoms. Stationary points were optimized at the UB3LYP/6-31G* level for model system A (16 heavy atoms) and at the UHF/6-31G* level for model system B (34 heavy atoms) with the GAUSSIAN03 program.[13] Density functional theoretical (DFT) calculations at the UB3LYP/6-31G* level have been shown to give reliable predictions for the energetics of hydrocarbon diradical species[12a,d,15] relative to those of other density functional methods (e.g., BPW91[11c]) or complete active space self-consistent field (SCF) methods.[12b–d,15d] UB3LYP/6-31G* enthalpies at 298 K and conductorlike polarizable continuum model (CPCM) solvation free energies[16] in H_2O were computed. Minimum energy reaction pathways were constructed for each of the proposed mechanisms.

Cleavage of the cyclobutane ring of dicationic sceptrin model $\mathbf{11}^{2+}$ to form the diradical species[17] analogous to $\mathbf{5}^{2+}$ requires 30.5 kcal mol^{-1}. A dicationic diradical intermediate analogous to $\mathbf{5}^{2+}$ is formed and is 6.8 kcal mol^{-1} more stable than the ring-opening transition state. This behavior is in contrast to the flat potential surfaces that are typical of hydrocarbon rearrangements that involve diradicals.[12,15] Coulombic repulsion between the cationic aminoimidazole rings of the reactant is relieved in the diradical intermediate, as the inter-aminoimidazolyl distance increases by 2.5 Å. Closure of the diradical requires 7.8 kcal mol^{-1} and gives the si product. The sr ring-closure transition state is 1.3 kcal mol^{-1} higher in energy than the si ring-closure transition state.

Ring opening of the monocationic[17] model compound $\mathbf{12}^{+}$ requires 35.8 kcal mol^{-1} and leads to a flat potential-energy surface, typical of the hydrocarbon

vinylcyclobutane rearrangement. The experimental ΔH^{+} value for the rearrangement of divinylcyclobutane to form vinylcyclohexene is 34.0 kcal mol^{-1},[18] while the same barrier computed with DFT is 31.3 kcal mol^{-1}.[12c] These results indicate that a 2-aminoimidazole group and a vinyl group stabilize a radical to nearly the same extent and led us to calculate radical stabilization energies (RSE) of 2-aminoimidazole, protonated 2-aminoimidazole, and 2-H imidazole. RSEs, calculated at the UB3LYP/6-31G* level relative to the allyl radical,[19] were found to be 2.5–3.9 kcal mol^{-1} lower than that of the allyl radical for all substituents, thus indicating no large difference in their ability to stabilize a radical. Both si and sr ring-closing transition states have been located for monocationic sceptrin model compound **12**$^{+}$; both are lower energy than the monocationic diradical intermediate (by 3.0 and 1.4 kcal mol^{-1}, respectively) when zero point energy and solvation are included.

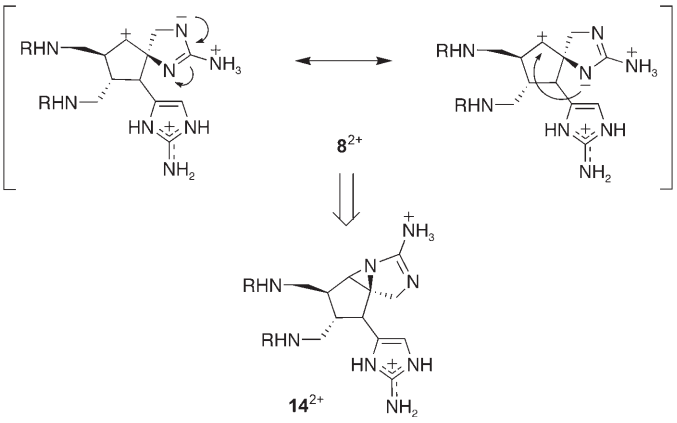
The ring opening of *trans*-1,2-di(4-imidazolyl)cyclobutane (Scheme 4), a neutral analogue of **11**$^{2+}$ and **12**$^{+}$, requires



Scheme 4. A) Microwave irradiation of the known allylurocanate dimer results in hydrolysis and no rearrangement. B) Model system of the neutral **1**$^{2+}$ analogue used in computational studies.

47.2 kcal mol^{-1}. Baran et al. have shown that exposure of the structurally similar allylurocanate dimer to microwave radiation at 200 °C in H_2O resulted in 100 % of the hydrolysis product and none of the rearrangement product, thus indicating the 2-aminoimidazolyl moiety of **1**$^{2+}$ is necessary for rearrangement.[4]

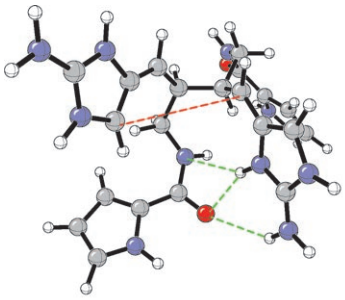
Computational studies of the dicationic multiple-shift mechanism were also performed. Formation of an intermediate species analogous to **7**$^{2+}$ is only 28.7 kcal mol^{-1} higher in energy than the starting sceptrin model compound **11**$^{2+}$. However, the subsequent [1,2] shift does not lead to the spiro intermediate **8**$^{2+}$, as postulated in Scheme 2c. Instead, all attempts to optimize the spiro intermediate model compound of **8**$^{2+}$ led to the tricyclic intermediate analogue of **14**$^{2+}$ shown in Scheme 5. Rearrangement through the multiple-shift mechanism via the analogue of **14**$^{2+}$ requires 37.7 kcal mol^{-1}, which exceeds the barriers to rearrangement of the monocationic **12**$^{+}$ and dicationic **11**$^{2+}$ model systems by 1.9 and 6.2 kcal mol^{-1}, respectively. Computations involving this model system indicate that the rearrangement of **1**$^{2+}$ most likely proceeds through a stepwise diradical process that starts from dicationic sceptrin (**1**$^{2+}$). It remains possible that two equivalents of **4**$^{+}$ may undergo a [2 + 2] dimerization to give **1**$^{2+}$, which can then rearrange to give **2**$^{2+}$ and **3**$^{2+}$. However, computations predict it to be unlikely for two equivalents of **4**$^{+}$ to react in a concerted [4 + 2] manner to give **2**$^{2+}$ or **3**$^{2+}$. The concerted transition state that leads to **2**$^{2+}$ and **3**$^{2+}$ from two equivalents of **4**$^{+}$ is 6 kcal mol^{-1} higher in energy than the stepwise diradical pathway. Additionally, Lindel and co-workers recently reported[20] the failure of oroidin, which is brominated **4**$^{+}$, to undergo Diels–Alder reactions to give dibromoageliferin.



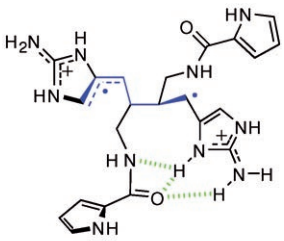
Scheme 5. The formation of the high-energy tricyclic intermediate **14**$^{2+}$ from structure **8**$^{2+}$ through the dicationic multiple-shift reaction pathway (Scheme 2C).

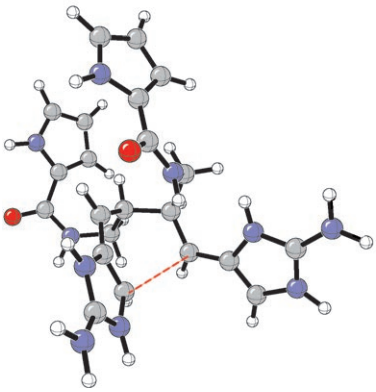
In the more complete model system B **13**$^{2+}$, the ring-closing transition states that lead to the sr and si rearranged products **3**$^{2+}$ and **2**$^{2+}$ were optimized at the UHF/6-31G* level. The effects of solvation by H_2O were computed with CPCM solvation calculations. The most noteworthy difference between the sr and si transition states is the existence of three hydrogen-bonding interactions present in the sr ring-closing transition state (Figure 1). These are not observed in the si ring-closing transition state that leads to **2**$^{2+}$. Ring closure to **3**$^{2+}$ is predicted to be 1.7 kcal mol^{-1} more favorable than formation of **2**$^{2+}$ on account of these stabilizing hydrogen-bonding interactions. This $\Delta\Delta H^{+}$ value predicts **3**$^{2+}$ to be preferentially formed over **2**$^{2+}$ in a ratio of 22:1, which is in good agreement with the experimental results. In both the si closing transition state and the resulting **2**$^{2+}$, the *trans* relationship between the migrating 2-aminoimidazolyl group and the pyrrole side chain α to the allylic radical renders them incapable of forming similar hydrogen-bonding interactions.

In summary, computational studies on the vinylcyclobutane rearrangements of sceptrin to ageliferin and nagelamide E lead to the conclusion that rearrangement occurs via diradical intermediates starting from dicationic sceptrin (**1**$^{2+}$). Hydrogen-bonding interactions present in the 6-*endo-trig* closing transition state favor the formation of the [1*r*,3*s*] product, ageliferin. We have also reported the first total synthesis of nagelamide E. The fact that nagelamide E and ageliferin are synthesized by thermal rearrangement in approximately the same ratio as they are isolated from nature is remarkable and suggests the possible involvement of a similar process in the biosynthesis of these compounds.



sr transition state (ageliferin)
$\Delta H_{rel} = 42.5$ kcal mol^{-1}





si transition state (nagelamide)
$\Delta H_{rel} = 44.2$ kcal mol^{-1}

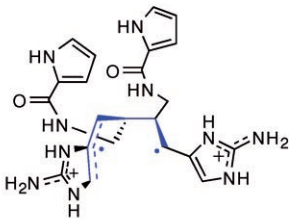


Figure 1. Optimized structures of the sr and si ring-closing transition states (model system B), which lead to $\mathbf{3}^{2+}$ and $\mathbf{2}^{2+}$, respectively. Dashed green lines indicate hydrogen-bonding interactions. Dashed red lines indicate the formation of covalent bonds. Bonds highlighted in blue (ChemDraw structures) indicate those that become the cyclohexene ring upon covalent bond formation.

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