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The Intramolecular Diels–Alder Reaction of Tryptamine-Derived Zincke Aldehydes Is a Stepwise Process

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Abstract

Computational studies show that the base-mediated intramolecular Diels–Alder of tryptamine-derived Zincke aldehydes, used as a key step in the synthesis of the *Strychnos* alkaloids norfluorourarine and strychnine, proceeds via a stepwise pathway. The experimentally determined importance of a potassium counterion in the base is explained by its ability to preorganize the Zincke aldehyde diene in an *s*-cis conformation suitable to bicyclization. Computation also supports the thermodynamic importance of the generation of a stable enolate in the final reaction step. The thermal cycloreversion reaction of the Diels–Alder products is also found to proceed in a stepwise manner.

Introduction

The Diels–Alder cycloaddition is one of the most important ring-forming reactions available to organic chemists.¹ Its impact on natural product synthesis, in both its inter- and intramolecular manifolds, cannot be overstated.² Mechanistically, these reactions must fall along the continuum linking the concerted synchronous pericyclic “ideal”, represented by the parent reaction of 1,3-butadiene with ethylene, and the stepwise Michael addition/aldol addition that is characteristic of processes with highly polarized reaction partners (Figure 1).³ Often, a stereochemical test can be used for detection of a stepwise mechanism for cycloaddition; observation of a lack of stereospecificity in a Diels–Alder reaction (correlation of the stereochemistry of the dienophile and/or the diene to that of the product) can be reasonably explained by the operation of a Michael/aldol pathway. For example, Jorgensen and coworkers have found that the purported Diels–Alder reaction in the enzyme-catalyzed reaction of macrophomate synthase is actually a two-step Michael/aldol process.^{3c}

Since the development of relatively accurate density functional methods, computations have become a useful vehicle for the determination of reaction mechanisms.⁴ Here we apply the methods of computational chemistry to establish the mechanisms of a particular class of Diels–Alder reactions that has demonstrated significant value in alkaloid synthesis.

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[†]Electronic Supplementary Information (ESI) available: Reaction coordinate diagram for the cycloaddition of the lithiated substrate corresponding to **5K**, and all B3LYP/6-31G(d) gas-phase geometries and M06-2X/6-311+G(d,p) total energies. See DOI: 10.1039/b000000x/

Background

In the course of a project aimed at the synthesis of indole monoterpene alkaloids, including norfluorocurarine (**1**, Scheme 1) and the classic target strychnine (**2**), two of us developed the intramolecular Diels–Alder (IMDA) reaction of tryptamine-derived Zincke aldehydes (**3** → **4**).^{5–7} This complexity-generating transformation was mediated by stoichiometric quantities of base (typically KO^tBu) and, in many cases, provided the cycloadducts in high yield. In every successful reaction, the product was formed as a single diastereomer and with conjugation of the unsaturated aldehyde. This conjugation event obscured one of the stereochemical readouts of this Diels–Alder reaction (the relative configuration of C3 and C16^x). The two dienophile-derived stereogenic centers (C2 and C7) can only be *cis*, because the dienophile is part of the five-membered ring of the indole.

There seemed no obvious experimental way to determine if this cycloaddition reaction of two highly polarized reaction partners proceeded via a stepwise Michael addition/Mannich addition cascade or an asynchronous yet concerted pericyclic process. These two mechanistic possibilities are shown in Scheme 2, and knowing which pathway was operative could permit broader application of this powerful reaction type.

At the outset, the stepwise process seemed entirely reasonable. We presumed that the strong base was metallating the indole. The resulting highly nucleophilic metalloenamine should be competent for intramolecular conjugate addition, even with the donor-acceptor diene, which demonstrates diminished electrophilicity relative to normal conjugate acceptors. A successful bicyclization reaction would require the conjugate addition reaction to engage the *s-cis* conformer of the Zincke aldehyde which, while certainly not its ground state, should be readily accessible. Meeting this requirement allows for the intermediate dienolate to be formed with the *Z* geometry required for the terminal Mannich reaction. We recognized that the conjugate addition reaction might well be reversible, and only when the *s-cis* conformer was participating, would the final tetracyclic product arise. Finally, on the basis of pK_a values, we assumed that the resulting metallated indoline would equilibrate to the dienolate shown,^y which should be the resting state of the product prior to aqueous workup.

The concerted (yet certainly asynchronous) cycloaddition possibility also held elements of attractiveness. Zincke aldehydes are known to be poor dienes in intermolecular Diels–Alder cycloadditions, no doubt as a result of their donor-acceptor stabilization.⁸ However, analysis of hand-held molecular models suggested that, for appropriate overlap of the participating π -systems, conjugation of the Zincke aldehyde nitrogen's unshared electron pair with the rest of the system would need to be compromised. In that situation, we surmised that the nitrogen atom would serve predominantly as an inductively electron-withdrawing group toward the $\alpha,\beta,\gamma,\delta$ -unsaturated aldehyde, resulting in a particularly electron-deficient diene. That π -system might well participate in a concerted yet asynchronous Diels–Alder reaction with the metallated indole C2–C3 bond, because the HOMO–LUMO gap might not be too large. We also considered the fact that the thermal requirements of the reaction (80 °C) might be related to the need to compromise conjugation in the Zincke aldehyde system.

To investigate this notion, HOMO and LUMO energies were calculated for the indole and Zincke aldehyde, respectively. Deprotonation of the indole affords a better electron donor, reflected by the 0.20 eV increase in the energy of the HOMO. In contrast, deconjugation of the nitrogen in the Zincke aldehyde lowers the LUMO energy by only 0.03 eV. Thus, the

^xWe use the so-called “biogenetic numbering” often used for the *Strychnos* alkaloids; J. Le Men and V. I. Taylor, *Experientia*, **1965**, *21*, 508.

^yAn interesting feature of this reaction is that the potentially destructive β -elimination pathways that could eject either nitrogen apparently do not lead to the formation of significant quantities of side products.

decrease in the HOMO-LUMO gap is mainly attributed to the indolyl anion and, to a much lesser extent, the amine deconjugation.

Because of the apparent feasibility of the two mechanisms, the importance of the reaction to our efforts in alkaloid synthesis, and the lack of obvious experiments to distinguish between the two possibilities, we looked to computation for a greater understanding of this process. This study ultimately revealed the importance of (1) the counterion of the base used to metallate the indole to the success of the reaction, and (2) the ability to form a stable enolate to drive this reaction forward. Furthermore, we have gained a greater comprehension of a fascinating cycloreversion process that occurs when the cycloadducts are converted to their corresponding iminium ions and heated. We have obtained detailed information about the mechanisms through density functional theory, and the results are consistent with available experimental data.

Results and Discussion

Stepwise versus concerted process?

Our first efforts sought to evaluate the feasibility of the concerted cycloaddition pathway of the *N*-metallated indole. However, a transition state for such a process could not be found; all efforts to locate a concerted transition state resulted in formation of only one of the C–C bonds, strongly suggesting that a stepwise process was at play. We considered the effect of the amine tether on the available conformations of the diene and dienophile. In order to determine if intramolecularity was preventing favorable orbital overlap for the cycloaddition to occur, an analogous bimolecular reaction was studied where the tether between the indole and Zincke aldehyde was severed. Nevertheless, a concerted transition state could not be attained. As shown in Figure 2, the C3–C7 bond is formed preferentially through a Michael addition. Therefore, the Michael/Mannich reaction sequence of the indole anion was modeled.

The reaction coordinate diagram for the stepwise Michael/Mannich reaction sequence is outlined in Figure 3. Optimizations were performed with the B3LYP density functional with a 6–31G* basis set in the gas phase.^{4b} Single-point energy calculations were then conducted on the optimized structures with the M06-2X functional, which includes nonlocal effects of electronic dispersion and has been shown to provide good estimates of energies for bond-forming reactions.^{4a} For computational simplicity, the *N*-allyl protecting group was replaced with a methyl. Using deprotonated indole **5** as our model system, a Michael addition through **TS_5–6** leads to spirocyclic dienolate **6**. The dienolate then undergoes an intramolecular Mannich reaction via **TS_6–7** to form indolate **7**. The tautomer, **8**, is considerably more stable.

Although the Zincke aldehyde of **5** is shown in its lowest energy *s-trans* conformation, it is clear that the double bond in the newly formed cyclohexene ring of **7** must adopt a *cis* configuration. This transformation can happen either through a conformational change of **5** from the *s-trans* to the *s-cis* conformation prior to C3–C7 bond formation, as shown in the energy profile, or by a *cis/trans* isomerization of **6** before proceeding to ring closure. Both transformations are facile under the experimental conditions and thus have energy barriers lower than that of **TS_5–6** and **TS_6–7**, implying that there are *cis/trans* and *s-cis/s-trans* equilibrations throughout the reaction pathway, but only the *cis* configurations of **6** will proceed to product.

The overall reaction has a 33.1 kcal/mol barrier in THF because of the loss of indole aromaticity. This high barrier is consistent with the elevated thermal conditions necessary for the reaction. M06-2X predicts the reaction to be unfavorable by 3.8 kcal/mol for the free

anion, but with the counterion included the reaction becomes favorable, as described in the next section.

In the experimental optimization of this cycloaddition, we found that only potassium bases mediated successful reactions. An extensive survey of bases included: (1) neutral amine and phosphazene bases; (2) lithium, sodium, potassium alkoxides and amides; (3) several metal hydrides; (4) Grignard reagents; and (5) several metal carbonates and phosphates.^{7,9} The results clearly demonstrated that potassium bases were uniquely effective, with the best outcomes arising from the use of commercially available 1.0 M solutions of KO^t-Bu in THF; the use of KHMDS and KH did lead to product formation, but with less efficiency. The inclusion of 18-crown-6 or polar solvents known to sequester alkali metal cations (NMP, DMPU, HMPA) completely prevented product formation, pointing to a critical role for this cation, and not simply a preference for more dissociated counterions. The failure of cesium carbonate circumstantially supports this idea. Accordingly, the Michael/Mannich reaction pathway was studied computationally starting from the *N*-potassiated indole.

As shown in Figure 3, the energy profile of the stepwise mechanism with coordination of a potassium counterion resembles that of the parent reaction, with an overall decrease in ΔG values for both gas phase and solvent calculations. The inclusion of this counterion results in a 27.9 kcal/mol activation barrier for the reaction in solvent, 5.2 kcal/mol lower than that of the parent IMDA. In addition, the equilibrium is now in favor of the forward reaction, consistent with the observed formation of bicyclized product. The potassium counterion stabilizes the enolate product more than the starting indolyl amide anion.

In an attempt to probe the uniqueness of potassium in this reaction, the IMDA was subsequently modeled with a lithium counterion. The lithiated complexes closely resemble the potassiated ones, and the cyclization is predicted to be favorable by 2.6 kcal/mol.⁹ At this time, we cannot offer any explanation for the lack of success of lithium bases in laboratory experiments. Because of the subtle differences between potassium and lithium and their propensity to participate in complexation with solvent molecules,¹⁰ a rigorous explicit-solvent model is necessary to explain the success of potassiated bases but not those derived from lithium, which would add a level of complexity to the computations that are outside the scope of this study.

One of the striking features of our results is the apparent “templating” effect of the potassium counterion which, when bound both covalently to the indole nitrogen and datively to the aldehyde oxygen, preorganizes the Zincke aldehyde for successful reaction. Evidently, the chelation of potassium to the substrate favors the adoption of the *s*-cis conformation of the Zincke aldehyde, which is a critical requirement for C3–C7 bond formation to lead to the requisite *Z*-configured dienolate intermediate. As stated above, for geometrical reasons, only the *Z*-dienolate can engage in the Mannich-type C2–C16 bond formation that generates the *Strychnos* E ring.

The importance of generating a stable dienolate

One of the features of this reaction that we had long considered to be important was the presumed equilibration of the initial cycloadduct **7K**, with its *N*-potassiated indoline, to the potassium dienolate **8K**. On pK_a grounds, we expected this acid-base reaction to be substantially favored. Certainly, the computational results shown above demonstrate that the cycloaddition reaction is not thermodynamically favored unless this equilibration is taken into account. We performed a simple experiment to further probe the importance of this process. The synthesis of α -methyl Zincke aldehyde **5aM** was accomplished in two steps from 3-picoline according to our established procedures.⁷ Attempted cycloaddition under the standard conditions led to exclusive recovery of starting material, and more forcing

conditions led to decomposition. These results are nicely supported by the computational results shown in Figure 4, which show the very endergonic nature of this reaction.

The IMDA reaction with the α -methyl Zincke aldehyde was modeled using M06-2X single point energies. Under the thermal reaction conditions, the ~ 13 kcal/mol barrier for cycloreversion is easy to traverse, resulting in a completely reversible reaction. Without the possibility of a stable enolate as a resting state for the product, the equilibrium strongly favors the starting material by 20.7 kcal/mol, consistent with the recovery of exclusively uncyclized reactant. Similar optimized geometries for the intermediates and transition states compared to the parent reaction suggest that the mechanism is not altered with the introduction of the methyl to the α position of the aldehyde. Calculations on the potassiated case present comparable results. Taken together, the computational and experimental results point to a large component of the exergonicity of these anionic cycloaddition reactions arising from the formation of a stable potassium dienolate after the C–C bond-forming steps of the sequence is complete.

Cycloreversion via iminium intermediates

In the course of an attempt to mediate D-ring formation in a projected route toward strychnine, we tried to induce C15–C20 bond formation by activation of the α,β -unsaturated aldehyde of aldehydes of type **4** ($R=CH_2C(SiMe_3)CHCH_3$) as its corresponding iminium ion (**9**, Scheme 3). We hoped that would make it susceptible to nucleophilic attack at the β -position by the tethered vinylsilane, as shown in **10**. Certainly, iminium ions are competent electrophiles in vinylsilane-terminated cyclizations, as pioneered by Overman,¹¹ and the MacMillan group has clearly demonstrated that α,β -unsaturated iminium ions are activated toward nucleophilic attack at the β -position.¹² Upon treatment of aldehyde **4** with pyrrolidine, the corresponding iminium ion **9** was observed by mass spectrometry. Heating the reaction mixture to 150 °C led to clean cycloreversion, and Zincke aldehyde **15** was recovered cleanly after aqueous workup. Some pyrrolidine-derived Zincke aldehyde (not shown) was also observed, from unselective hydrolysis of unsymmetrical iminium ion intermediate **12**. This result clearly demonstrated that the cycloaddition/cycloreversion equilibrium could be perturbed under different conditions. This reaction might also proceed via either a stepwise or a concerted pericyclic process, and we turned to computation to determine its likely course.

Figure 5 exhibits the computed energetics for possible ring-opening pathways. Each pathway was calculated using the B3LYP/6–31G* basis set, with all optimizations conducted in THF solvent. As before, M06-2X single point energies were then calculated in the gas phase and corrected using the CPCM solvent model. After formation of unsaturated iminium ion **9**, an alkene isomerization provides intermediate **11** which can then cyclorevert through a concerted retro-Diels–Alder reaction or a stepwise retro-Mannich/retro-Michael sequence via **13** to attain Zincke aldehyde **12**. A third possible pathway involves the retro-Mannich occurring before the isomerization, yielding allenamine **14** before continuing on to intermediate **13** in the previously mentioned stepwise pathway. A concerted transition state leading directly to the cycloreverted product could not be found.

As shown in Figure 5, formation of allenamine **14** requires 42.0 kcal/mol, a much higher barrier compared with the pathway involving alkene isomerization. Thus, it is unlikely that this pathway occurs, but rather isomerization to form intermediate **11** takes place initially. The absence of a concerted transition state once again suggests a stepwise mechanism. Imine **11** can proceed to cycloreversion product **12** through intermediate **13**, following a pathway reminiscent of the forward reaction studied earlier.

In short, while the tryptamine-derived Zincke aldehyde cycloaddition is driven forward under basic conditions by the formation of a stable enolate (despite the loss of aromaticity in the indole five-membered ring and the donor-acceptor stabilization of the Zincke aldehyde), the cycloreversion is favored by the formation of the aldiminium ion, which leads to regeneration of indole aromaticity and the generation of the highly resonance-stabilized donor-acceptor iminium ion. This system provides a rare example of the ability to completely control the Diels–Alder cycloaddition/cycloreversion equilibrium based upon the choice of reaction conditions.

Conclusions

Through computation, we have developed a much deeper understanding of the key anionic cycloaddition reaction that facilitated concise syntheses of several *Strychnos* alkaloids, including norfluorocurarine and strychnine. This transformation occurs through a stepwise Michael/Mannich cascade rather than a concerted Diels–Alder cycloaddition. This reaction proceeds only when the indole is metallated with potassium bases, and computation has attributed this particularity to potassium's ability to pre-organize the aldehyde in an *s-cis* manner, providing the appropriate conformation for successful reaction. The driving force for the reaction is the formation of a stable potassium enolate as a resting state for the cyclized product. When the possibility of formation of such a low-energy enolate is removed, the reaction does not proceed because the equilibrium favors starting material.

Formation of an unsaturated iminium ion in attempts to install the D-ring of the *Strychnos* alkaloids caused an unexpected cycloreversion that unravels the B- and C-rings. Ring opening proceeded through a stepwise retro-Mannich/retro-Michael cascade, related to the mechanism of forward cycloaddition. This delicate equilibrium between cycloaddition and cycloreversion allows for manipulation of reaction conditions to achieve either outcome.

The greater understanding of the mechanism of this important Diels–Alder-type reaction of Zincke aldehydes will enable broadening of the scope of these complexity-generating transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The mechanistic continuum of Diels–Alder cycloadditions

Figure 2. Modeling the intermolecular reaction between indolate and Zincke aldehyde. The forming C-C bond is shown in gray. The N-allyl protecting group was modeled by a methyl group.

Figure 3.

Energy profiles for the IMDA of the anion and the potassium salt. ΔG values were calculated using M06-2X/6-311+G** single-point energies with B3LYP/6-31G* optimized structures in the gas phase. Corrections with the CPCM model of THF solvent are in parentheses.

Figure 4.

Energy profile of IMDA reaction with alpha-methylated Zincke aldehyde. ΔG values calculated using M06-2X/6-311+G** with CPCM THF solvent for the parent reaction (blue) and potassium-assisted reaction (purple)

Figure 5.

Energy profile for various pathways of cycloreversion. ΔG values were calculated using M06-2X/6-311+G** single-point energies with B3LYP/6-31G* optimized structures in the gas phase. Corrections with the CPCM model of THF solvent are in parentheses. Isomerizations (gray) were not explicitly calculated

Scheme 1.

Base-mediated IMDA reaction of tryptamine-derived Zincke aldehydes was a key step in norfluorocurarine and strychnine syntheses

Stepwise:

1. Intermediate dienolate must have a *cis* geometry, arising from an *s-cis* Zincke aldehyde
2. The reaction could be driven by the formation of stable enolate

Concerted:

For proper orbital overlap, the Zincke aldehyde nitrogen's non-bonded electron pair cannot remain conjugated with the rest of the π -system

Scheme 2.

Two reasonable mechanistic possibilities for the intramolecular Diels–Alder cycloaddition of tryptamine-derived Zincke aldehydes

Scheme 3. Possible mechanisms for cycloreversion and regeneration of Zincke aldehyde **15**