

Mechanism of *cis*-Enamide Formation from *N*-(α -Silyl)allyl Amides: Synthetic Potential of Stepwise Dyotropic Rearrangements

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Abstract: A novel transformation of silyl amides to *N-cis*-propenyl amides was recently reported, the reaction of which is a formal 10-electron double sigmatropic, or dyotropic, rearrangement. Density functional calculations (B3LYP/6-311++G(3d,3p)//B3LYP/6-31G(d)) have been carried out to investigate the mechanism of this reaction. A two-step process involving sequential 1,4-silyl and 1,4-hydrogen shifts is predicted. The 1,3-dipolar azomethine ylide intermediate profits from charge stabilization by allylic resonance and phenyl conjugation. The consecutive thermal migration of two σ -bonds (stepwise dyotropic rearrangement) is an example of a host of reactions with synthetic potential.

Introduction

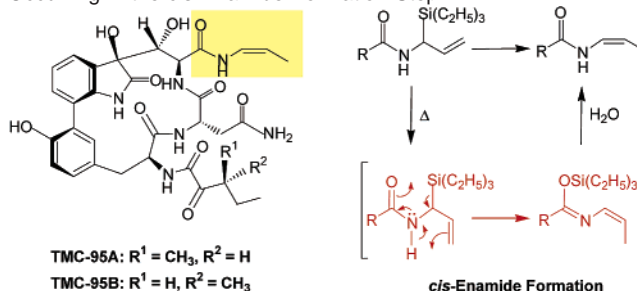
Recently, Lin and Danishefsky reported the first total synthesis of two promising drug candidates, TMC-95A and TMC-95B (Scheme 1).¹ A highlight of this work was the construction of a *cis*-enamide group near the end of the synthesis without affecting other functionalities. This was realized through the reorganization of a α -silylallyl amide protecting group upon heating at 140 °C in *o*-xylene for 3 days.

The mechanism of the *cis*-enamide formation step is the subject of the study described here. The reaction is a formal dyotropic 10-electron process² involving the simultaneous migration of two σ -bonds (C–Si and N–H). However, no direct experimental or theoretical evidence was advanced concerning the degree of concertedness of this reaction. Even the intramolecular nature of this reaction was not established. Density functional calculations reported here predict a novel two-step process involving sequential 1,4-silyl and 1,4-hydrogen shifts. This transformation could be a forerunner of synthetic transformations triggered by a relatively facile σ -bond migration.

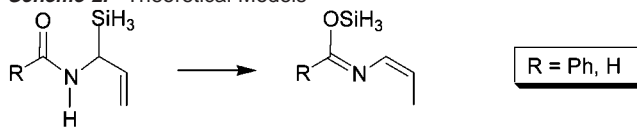
Computational Methods

Experiments on model systems have shown that when R is an aryl group (e.g., Ph) (Scheme 1), the lowest reaction time (10 h) is required, and the highest yield (81%) is achieved.¹ In contrast, when R is an alkyl group, a much longer reaction time (>3 d) is required for an acceptable yield.¹ Therefore, two model systems were studied theoret-

Scheme 1. TMC-95A, TMC-95B and the Bonding Changes Occurring in the *cis*-Enamide Formation Step



Scheme 2. Theoretical Models



cally with R = Ph or H (Scheme 2). In the theoretical models, –SiH₃ group is used instead of –Si(C₂H₅)₃ to simplify the calculations. This should not significantly influence the energetics.

B3LYP/6-31G(d) has been found to be a suitable method and basis set for general pericyclic reactions.³ Therefore, B3LYP/6-31G(d) geometry optimizations were carried out with Gaussian 98⁴ for the

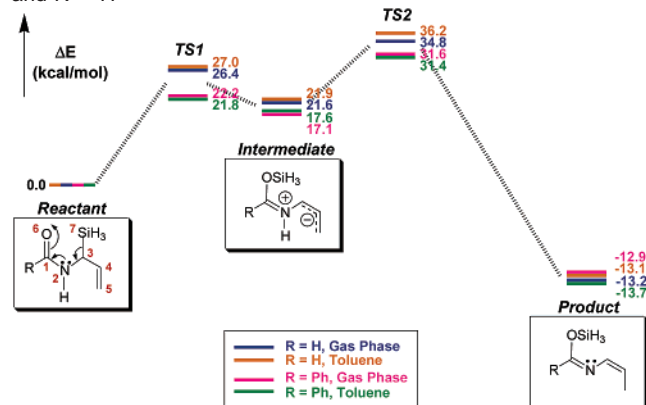
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Scheme 3. Energetics Computed for the Reactions When R = Ph and R = H



model systems in the gas phase. Frequency calculations were performed to verify the nature of all the stationary points as either minima or transition states and to provide zero point energy corrections. Single point energies and dipole moments were calculated at the more accurate B3LYP/6-311++G(3d,3p) level. Because the reactions were carried out in aromatic solvents (toluene or *o*-xylene),¹ solvation calculations were performed using the CPCM model⁵ to estimate the solvent effect upon energetics. Geometries from gas phase calculations were used directly because it is assumed that solvation will not dramatically change the geometries.

Results and Discussion

The calculated reaction pathways are shown in Scheme 3. For both of the model systems, with R = Ph or H, the same mechanism is followed. The reactions were found to occur by a stepwise mechanism with the formation of 1,3-dipolar azomethine ylide intermediates. The 1,4-silyl shift transition states (TS1) and 1,4-hydrogen shift transition states (TS2) were located and lead to the intermediates and the imidate products, respectively.

When R = Ph, the reactant has a conformation conducive to the silyl shift: O6 and C1–C3 are nearly coplanar, and the electropositive silyl group is facing the electronegative carbonyl oxygen (Figure 1). The N2–H group is in position to migrate also, but is 3.0 Å from C5. Another conformation of the reactant with the N2–H group trans with the C4=C5 group was also calculated, which is around 0.1 kcal/mol lower in energy than the cis one. This indicates that the rotation of the C3–C4 bond is facile. TS1 is very “late”, and has nearly complete bond formation between O6 and Si7. The silyl group migrates well out of the plane in a typical pericyclic sense. The zwitterionic is a typical azomethine ylide 1,3-dipole stabilized by the phenyl group. The identical bond distances (1.4 Å) of N2–C3, C3–C4, and C4–C5 indicate the importance of allylic resonance in the intermediate. The electropositive (N2)H now approaches the electronegative C5 (2.6 Å), promoting the second-step hydrogen shift. In TS2, N2, C3, C4, C5, and (C5)H are nearly coplanar and (C5)H is migrating between N2 and C5. The calculations suggest that the latter 1,4-hydrogen shift is the rate-determining step, which gives the product with a planar geometry except for the silyl group. The overall activation barrier for the reaction (31.4 kcal/mol) is typical for simple pericyclic processes (e.g., the Cope and Claisen rearrangements).⁶ Electrostatic potential

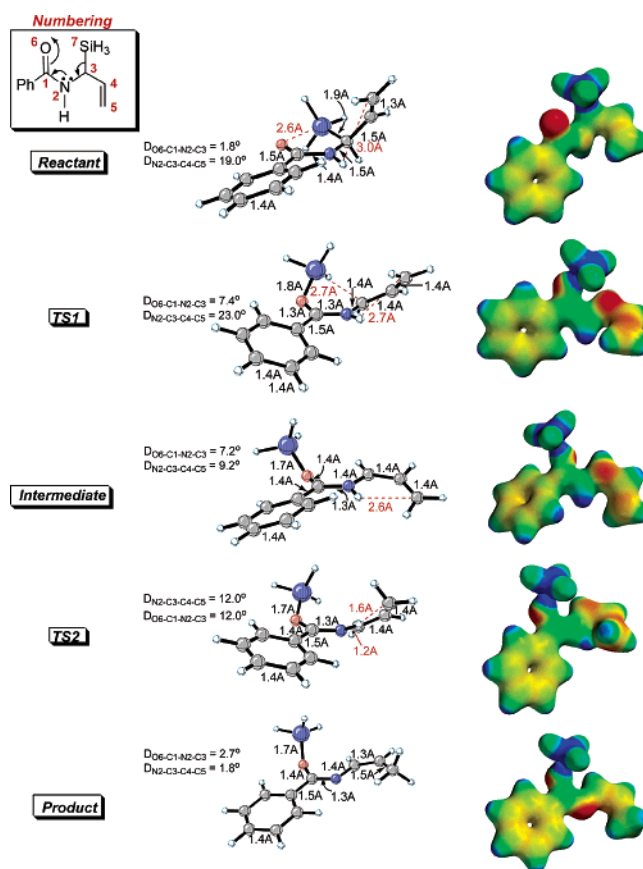


Figure 1. Computed geometries and electrostatic potential surfaces (blue and red represent positive and negative electrostatic potentials, respectively) with R = Ph.

surfaces were also calculated on the B3LYP/6-31G(d) geometries using HF/6-31G(d) in Spartan,⁷ as shown in Figure 1. It is noteworthy that no substantial charge separation is observed for the azomethine ylide intermediate compared to the reactant, product and transition states (TS1 and TS2), despite the formal charge separation in the 1,3-dipolar intermediate.

When R = H, the relative energies of TS1, TS2 and the intermediate increase by 3–5 kcal/mol, in the absence of stabilization of partial charges by Ph (Figure 2). This agrees with experiment, where a much longer reaction time is required when R is an alkyl group. Similar geometries of the reactant, intermediate, product, and transition states are followed except for the orientation of the siloxy group (O6–Si) in TS2 and the product (Figure 2). When R = Ph, the siloxy group is nearly orthogonal to the C1–Ph group, whereas when R = H, the siloxy group is cis and nearly coplanar with the C1–H group. This could result from the much less steric repulsion between silyl and H than that between silyl and Ph.

A dyotropic 10-electron rearrangement was noted as a formal possibility earlier,¹ but a concerted transition state could not be located for this overall thermally allowed process. Geometries constrained to induce concerted silyl and hydrogen shifts always converted into TS1 or TS2 after optimizations. A reaction

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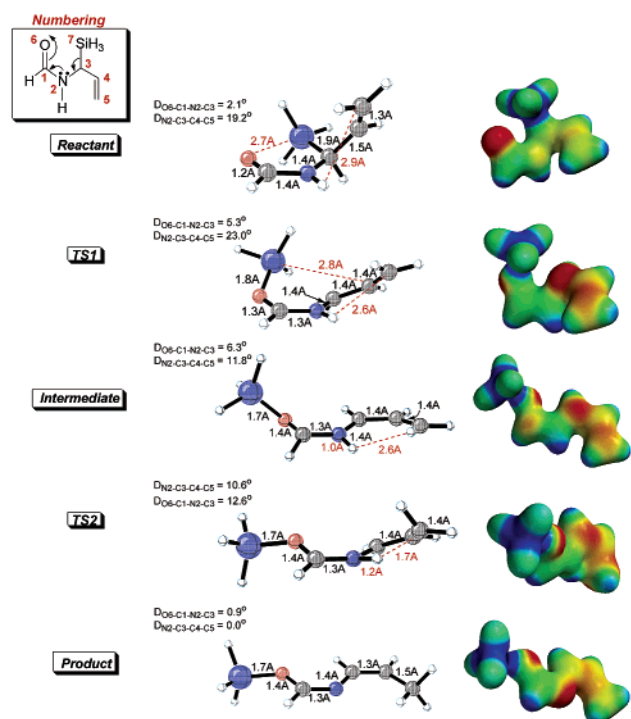
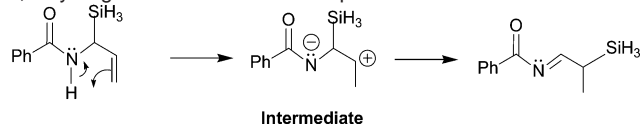


Figure 2. Computed geometries and electrostatic potential surfaces (blue and red represent positive and negative electrostatic potentials, respectively) with R = H.

Scheme 4. An Alternative Unfavorable Mechanism Involving 1,4-Hydrogen Shift as the First Step



coordinate scan did not locate a concerted transition state. The high demands of geometry organization for a concerted transition state may cause it to be unfavorable.

An initial 1,4-hydrogen shift could, in principle, initiate an alternative stepwise mechanism. Calculations indicate that the zwitterionic intermediate formed after hydrogen shift is highly unstable and would instantly convert into another product, which was not observed experimentally (Scheme 4).¹ The stronger migratory tendencies of silyl groups than hydrogen are well documented,⁸ and the facile formation of azomethine ylides by 1,2-silyl shifts has been noted previously.⁹

Calculations predict that toluene, the solvent used experimentally, affects the energetics only slightly. The relative energies of the zwitterionic intermediates show only a slight increase upon solvation even though they have formal charge separation. Stabilization by solvent is determined primarily by the dipole moments of molecules along with specific effects such as hydrogen bonding interactions and that are not included in the CPCM calculations. The calculated dipole moments of the reactant, intermediate, product, and transition states are found to be small and similar (Table 1), so that toluene does not affect the relative energies substantially.

When dyotropic rearrangements were defined by Reetz in 1972 as processes in which two σ -bonds migrate simultaneously,

Table 1. Dipole Moments with B3LYP/6-311++G(3d,3p)//B3LYP/6-31G(d) Calculations (Gas Phase)

	reactant	TS1	intermediate	TS2	product
R = Ph	4.2	3.1	1.7	1.5	0.9
R = H	3.7	2.3	2.2	3.2	1.8

they were discussed as two types: type I includes reactions in which the two σ -bonds interchange their positions, whereas in type II processes no direct positional interchange occurs.² Since then, high-energy or thermally forbidden dyotropic rearrangements have been postulated for various reactions with formal two σ -bond migrations,¹⁰ although the concertedness of most of these reactions was not established theoretically or experimentally. The stepwise dyotropic rearrangements determined here for the *cis*-enamide formation suggest that many of these reactions may occur sequentially. Among the reactions named as dyotropic rearrangements before, some involve reactions in which the two migratory groups and the two terminal atoms are of the same type (homotopic), and some involve different migratory groups or terminal atoms (heterotopic). Some typical examples for these two classes are shown in Scheme 5.¹⁰ Concerted dyotropic processes as defined by Reetz seem more likely in the homotopic cases because the potential intermediate is less stabilized than the concerted transition state. In each case, a concerted transition state could be located with C_s symmetry. In contrast, heterotopic reactions are likely to be nonconcerted dyotropic processes, because the migratory tendencies of the two σ -bonds are different and relatively stable species, like the azomethine intermediate, can form. When relatively stable intermediates form, thermally allowed stepwise dyotropic rearrangements will occur with lower activation energies than the corresponding concerted processes. The vitamin B₁₂ coenzyme-mediated reactions, heterotopic rearrangements in nature, can also be considered as stepwise dyotropic processes.¹¹

The process involving sequential silyl-hydrogen shifts determined here for the *cis*-enamide formation implies a new class of synthetic reactions. It is postulated that a series of molecules with the general structure shown in Scheme 6 may undergo similar stepwise dyotropic rearrangements. Besides the exothermicity of these reactions (formation of conjugated products with lower energies than the reactants), these reactions would be kinetically favored by a comparatively facile sigmatropic rearrangement to form a 1,3-dipolar azomethine ylide or carbonyl ylide intermediate. X requires lone electron pairs to form the crucial intermediate. When X = Y, A = B, R¹ = R², and R = R', concerted dyotropic rearrangements are likely without the formation of the intermediate unless many geometry demands are needed.

Conclusions

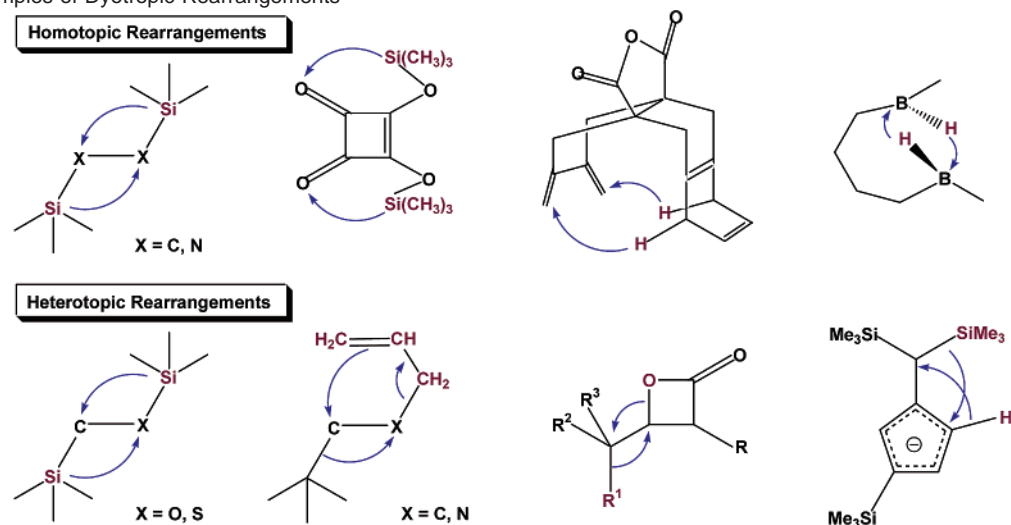
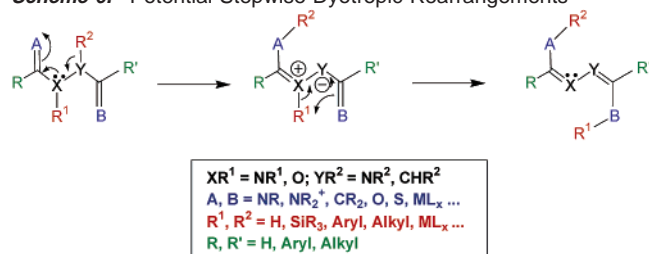
Computational studies predict a stepwise dyotropic rearrangement for the *cis*-enamide formation reported by Lin and Danishefsky. The stepwise dyotropic rearrangement involves a

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Scheme 5. Examples of Dyotropic Rearrangements¹⁰**Scheme 6.** Potential Stepwise Dyotropic Rearrangements

fast and reversible 1,4-silyl shift followed by a rate-determining 1,4-hydrogen shift. A concerted dyotropic mechanism is not competitive, according to the calculations. Solvent does not play a substantial role in the dyotropic reaction as a result of minor variations of polarity along the reaction pathway. It is proposed

that stepwise dyotropic rearrangements should be considered as possible reaction modes in principle, which requires lower activation energies than concerted processes. Finally, a host of reactions following a stepwise dyotropic mechanism are postulated that may be useful in synthesis.

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Supporting Information Available: Cartesian coordinates of all reported structures, as well as the total electronic and zero-point vibrational energies (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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