



Analyzing Kirby's amine olefin—a model for amino acid ammonia lyases

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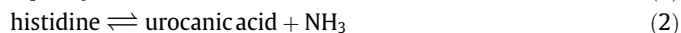
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ABSTRACT

Ab initio and DFT calculations on the ring-closing reaction of Kirby's amine olefin (ammonia lyase enzyme model) reveal that the process involves two consecutive steps: proton transfer from a molecule of water to the carbon–carbon double bond followed by nucleophilic attack of the amine nitrogen onto the second carbon of the double bond. Further, they indicate that the second step in the process is barrier less due to the combination of the release in strain energy upon conversion of the reactant to the product and, the proximity orientation of the nucleophile to the electrophile. Effective molarity (EM) calculations establish that Kirby's amine olefin process undergoes ring-closing at a rate that is comparable to the rates of reactions catalyzed by the most efficient enzymes.

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Ammonia lyases are enzymes that catalyze cleavage reactions of carbon–nitrogen bonds. The reactions catalyzed by lyase enzymes have been shown to be reversible. For example, phenylalanine ammonia lyase and histidine ammonia lyase enzymes catalyze the overall addition of ammonia to an unactivated double bond (Eqs. 1 and 2).¹



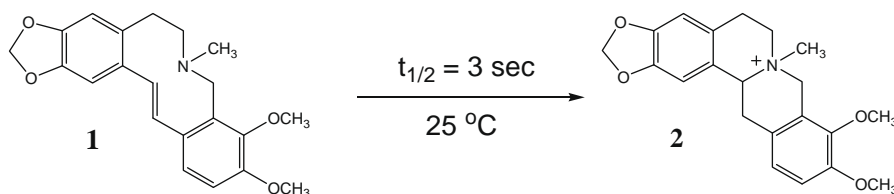
A number of studies have been carried out to explore the mechanism(s) by which lyase enzymes exert their high catalytic activities. Among the first studies was the addition reaction of aqueous ammonia to a fumarate dianion (an activated double bond moiety) by Bada and Miller. Their results indicated that the half-life for the deamination of aspartate (the reverse reaction) was nearly two weeks when the reaction temperature was set at 100 °C.²

Later, in 1978, Kirby reported the first lyases enzyme model which exhibited a spectacular rate under mild conditions with an effective molarity (EM) expected to exceed 10⁸ M.

Kirby's model has a molecular framework that holds two groups, an amino group, and an unactivated carbon–carbon double bond, at bonding distances. Juxtaposition of the two reactive groups in **1** leads to rapid addition of the amine to the carbon–carbon double bond yielding **2**. It was presumed that the reaction takes place due to activation by ground state strain (Scheme 1).³

This study on the reaction of **1** stems from a continued interest in the mechanisms of action of a variety of intramolecular processes that have been utilized as enzyme models.⁴

Recently, by exploiting the HF and DFT molecular orbital methods at different levels, we have investigated the acid-catalyzed lactonization of hydroxy-acids as studied by Cohen⁵ and Menger,⁶ the ring-closing reactions of di-carboxylic semi-esters as studied by Bruice,⁷ intramolecular proton-transfers in rigid systems as studied by Menger,⁶ and S_N2-based ring closure reactions as reported by Mandolini and Brown.⁸ The conclusions emerging from these studies are as follows: (1) both factors, ground state strain and proximity orientation of the two reactive centers, are important in accelerating the rate of an intramolecular process, depend-



Scheme 1. Intramolecular reaction of amine olefin **1** to yield cyclic product **2**.

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ing on the nature of the system. (2) The distance between the two reactive centers in an intramolecular reaction is a crucial factor in determining whether the reaction is inter- or intramolecular. (3) In S_N2 -based ring-closing reactions leading to three-, four-, and five-membered rings, the *gem*-dialkyl effect is more dominant than in the formation of an unstrained five-membered ring, and the need for directional flexibility decreases with the increasing size of the ring being formed. In addition, the demands on directional flexibility decrease on increasing the volume of the nucleophile involved in the S_N2 ring-closing reaction. (4) Enthalpic as well as entropic effects are both important factors in enhancing the rate of the intramolecular process. This is contrary to Bruice's proposal that indicates that enthalpic effects are the main driving forces for such accelerations.⁷

In this Letter, we describe our DFT and ab initio quantum molecular orbital investigations of transition state structures, vibrational frequencies, and gas phase reaction trajectories for the conversion of amine olefin **1** into cyclic product **2** and compare it to the corresponding intermolecular reaction, as well as to other intramolecular ring-closing reactions of amine olefins.

It is well known that the rate-limiting step in the addition reactions of HX (where X = halide, OH or NH_2) to an unsaturated carbon-carbon double bond is the addition of an electrophile, H^+ , to the double bond followed by a fast step in which a nucleophile X^- attacks an intermediate carbocation to furnish a saturated product. This type of reaction can occur under mild conditions. In contrast, the intermolecular reaction of an amine with an unactivated carbon-carbon double bond is not feasible even under harsh conditions. On the other hand, intramolecular ring-closing reactions of some 4- and 5-dimethylaminoalkenes such as **3** to give cyclic products **4** (major) and **5** (minor) are possible on boiling in acetic acid for a few hours (Scheme 2). This is similar to the ring-closing reaction of Kirby's amine olefin **1**, with the only exception being that the intramolecular process for **3** requires acidic conditions and heat, whereas that for **1** occurs under neutral or basic conditions at 25 °C.⁹

The goal of the study reported herein was to investigate all possible mechanistic pathways for the reaction of **1** and to unravel the nature of the driving force(s) for the unprecedented intramolecular addition of a nucleophile, an amine nitrogen, to an unactivated carbon-carbon double bond, such as that in **1**.

To simplify and reduce computational time, amine olefin **6**, corresponding to the amine olefin **1** employed in Kirby's kinetic study, was used in all the calculations.

Computational efforts in this study have been directed toward the elucidation of the transition states for all the possible pathways for the intramolecular ring-closing reaction of **6** to **7**.

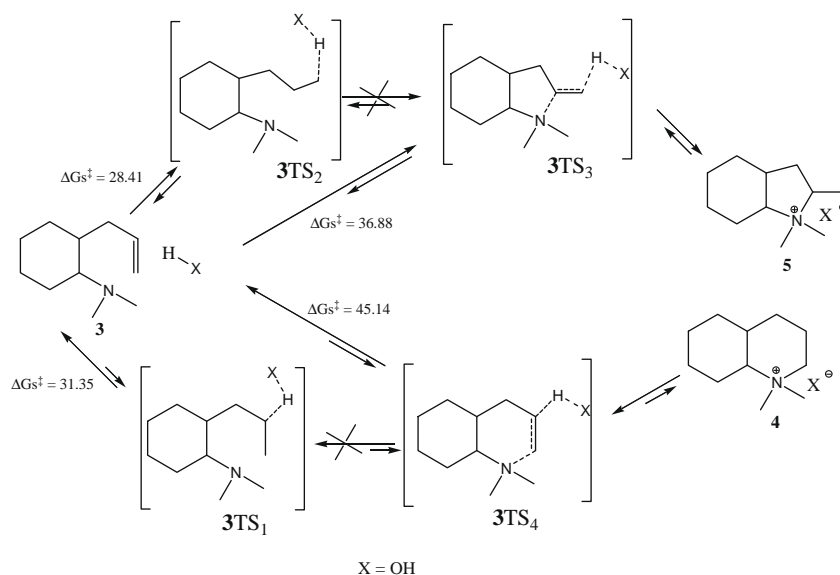
Using the quantum chemical package GAUSSIAN-98¹⁰ we have calculated the HF/6-31G and DFT B3LYP/6-31G (d,p) kinetic and thermodynamic parameters for all possible pathways for the reaction of **6**. The three possible paths for the ring-closing reaction of **6** are illustrated in Scheme 3 (for details of the calculation methods, see Supplementary data).

The calculated HF and DFT enthalpic and entropic energies for the global minimum structure (GM) and the four different transition states, TS_1 , TS_2 , TS_3 , and TS_4 for the suggested pathways in **6** (Scheme 3) are summarized in Table 1. Figure 1 illustrates the DFT-optimized calculated structures for GM, TS_1 , TS_2 , TS_3 , and TS_4 of **6**.

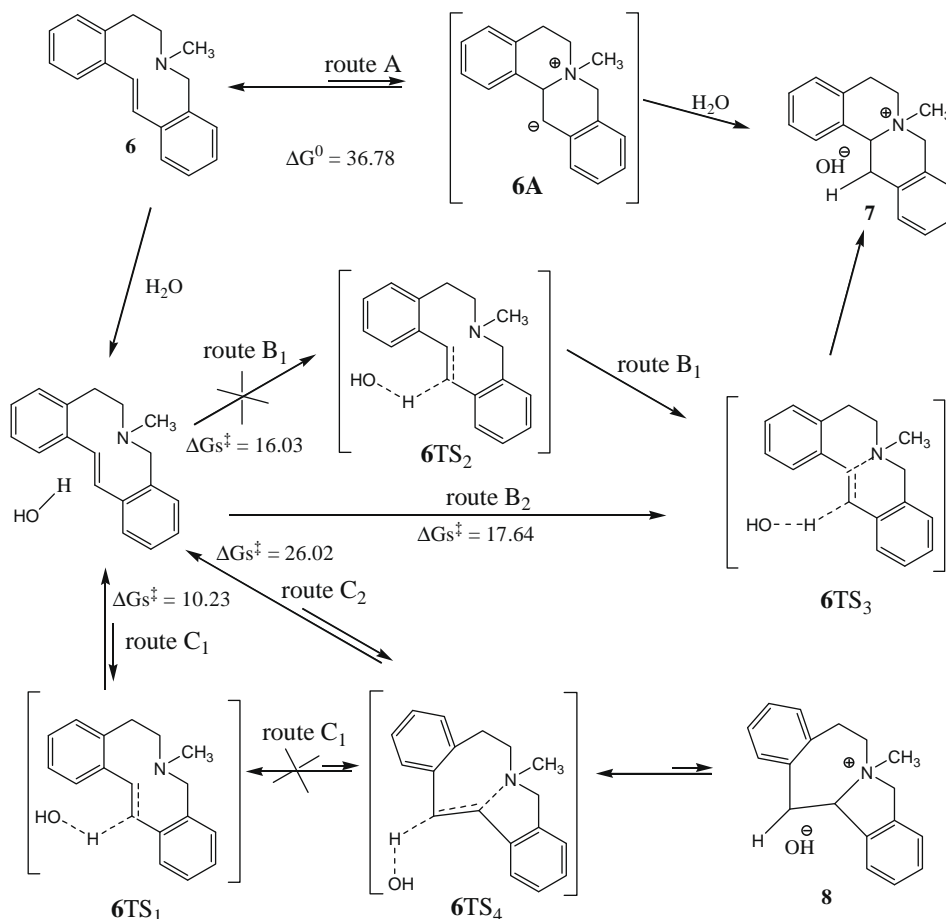
Using the calculated enthalpies and entropies for the GM and the transition states in **6** (Table 1), we have calculated the enthalpic activation energies (ΔH^\ddagger), entropic activation energies ($T\Delta S^\ddagger$), and the free activation energies in the gas phase (ΔG^\ddagger) and in water (ΔG_s^\ddagger) for the different paths (Scheme 3). The calculated values are summarized in Table 2.

The results depicted in Scheme 3 and listed in Table 2 indicate that the activation energy barrier for the ring-closing reaction of **6** via route B is the smallest among the other routes (A–C). For example, the calculated B3LYP/6-31G (d,p) activation energy value via route B is about 8.5 kcal/mol less than that via route C (17.64 kcal/mol vs 26.01 kcal/mol). Furthermore, the DFT calculation results for route A reveal that structure **6** is 36.78 kcal/mol more stable than structure **6A**, and that the latter undergoes cleavage back to **6** without activation. In other words, the barrier for the conversion of **6** into **6A** is more than 36 kcal/mol. This excludes the possibility that product **7** could be obtained via route A.

In order to examine whether the reaction mechanism involves route B_1 or B_2 , DFT calculations were undertaken to search for an intermediate between the region of the two transition states 6TS_2 and 6TS_3 , but failed to provide a minimum structure with an energy that was less than either of the transition state energies. In addition, the reaction coordinate for an approach of the amine nitrogen to



Scheme 2. Intramolecular reaction of amine olefin **3** to yield cyclic products **4** and **5**. The activation energy values are in kcal/mol. The DFT calculations were run for X = OH but are also applicable for other anions such as X = OAc.



Scheme 3. The three possible routes A–C for the intramolecular reaction of amine olefin **6**. The energy values are in kcal/mol.

ward the carbon of the double bond revealed that the energy needed to convert **6TS**₂ to **6TS**₃ is more than 10 kcal/mol. This result suggests that the limiting step for the addition reaction of the amine nitrogen to the carbon–carbon double bond in **6** is via route B₂: approach of a proton from a molecule of water toward one of the carbon atoms of the double bond concerted with nucleophilic attack of the amine nitrogen onto the other carbon of the double bond.

To shed light on the factors responsible for the unusual addition reaction of an amine nucleophile to a carbon–carbon double bond,

energy calculations for 5-dimethylaminoalkene **3** have been performed in the same manner as those for **6**. The calculation results which are summarized in Tables 1 and 2, and illustrated in Scheme 2 indicate that **3** undergoes ring-closing via a similar mechanism to that of **6**. However, in the case of **3** two possible cyclic products, **4** and **5**, could be obtained via two different transition states (**3TS**₂ and **3TS**₄). The calculated B3LYP/6-31G (d,p)/H₂O activation energy via **3TS**₂ is 8.26 kcal/mol smaller than that via **3TS**₄ (45.14 kcal/mol vs 36.88 kcal/mol).

Table 1
HF and DFT calculated properties for the reactions of **3**, **6**, **9**, and **11**

Compound	HF enthalpy, H (gas phase) in hartree	HF (gas phase) (entropy, S, Cal/Mol Kelvin)	HF frequency Cm ⁻¹	B3LYP enthalpy, H (gas phase) in hartree	B3LYP (gas phase) entropy, S, Cal/Mol Kelvin	B3LYP frequency Cm ⁻¹
3GM	-558.9657759	131.46	—	-562.9863293	131.51	—
3TS ₁	-558.8770775	105.48	1518.18i	-562.9218378	116.68	1070.16i
3TS ₂	-558.8474905	106.66	1358.12i	-562.8975722	112.40	790.28i
6GM	-822.8045711	139.47	—	-828.5197429	128.34	—
6TS ₁	-822.7495638	128.48	121.37i	-828.4844972	132.80	138.79i
6TS ₂	-822.7523661	130.41	517.92i	-828.7593143	133.14	205.53i
6TS ₃	-822.7394422	123.24	1407.35i	-828.4737269	129.95	834.68i
6TS ₄	—	—	—	-828.4556839	126.79	906.11i
9GM	—	—	—	-829.7503764	159.83	—
9TS ₁	—	—	—	-829.7084814	148.26	64.40i
9TS ₂	—	—	—	-829.6693544	135.19	782.94i
11GM	—	—	—	-791.6507722	124.27	—
11TS ₁	—	—	—	-791.6029091	163.71	57.71i
11TS ₂	—	—	—	-791.5527612	145.15	663.04i

HF and B3LYP refer to values calculated by HF/6-31G and B3LYP/6-31G (d,p), respectively. GM, TS₁, TS₂, TS₃, and TS₄ are global minimum and transition state structures, respectively.

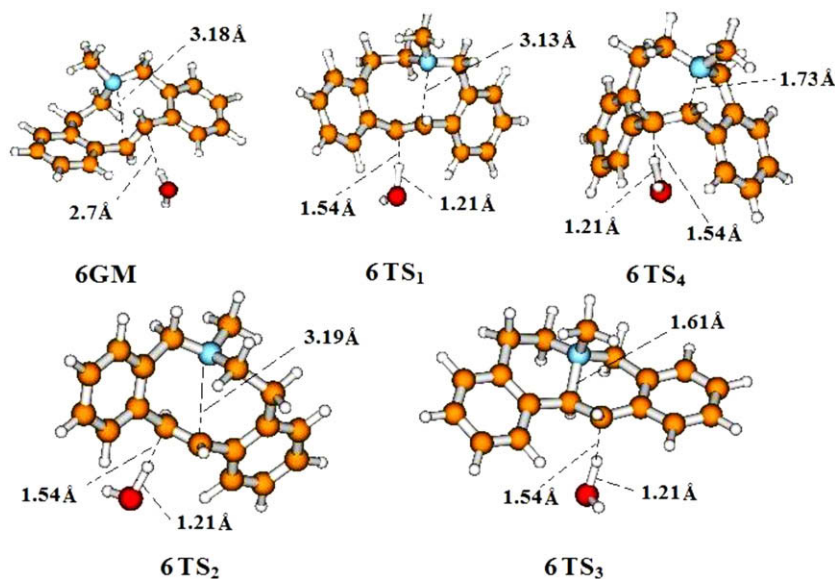


Figure 1. DFT-optimized structures for the global minimum structure (**6GM**) and the four possible transition state structures (**6TS₁**, **6TS₂**, **6TS₃**, and **6TS₄**) in the closing reaction of **6**.

Table 2

HF, DFT, and MM2 calculated kinetic and thermodynamic properties for the nucleophilic addition reactions in **3**, **6**, **9**, and **11**

System	Medium	MM2 ΔE_s	HF ΔH^\ddagger	HF $T\Delta S^\ddagger$	HF ΔG^\ddagger	B3LYP ΔH^\ddagger	B3LYP $T\Delta S^\ddagger$	B3LYP ΔG^\ddagger
3	Gas phase	11.52	50.22	-6.59	56.81	40.49	-4.41	44.90
	Water		39.21	-6.59	45.80	32.47	-4.41	36.88
6	Gas phase	-2.93	40.87	-4.84	45.71	28.88	0.48	28.40
	Water		25.66	-4.84	30.50	16.51	0.48	16.03
9	Gas phase	17.07	—	—	—	50.83	-7.34	58.17
	Water		—	—	—	39.53	-7.34	46.87
11	Gas phase	17.95	—	—	—	61.48	-6.22	67.70
	Water		—	—	—	45.94	-6.22	52.16

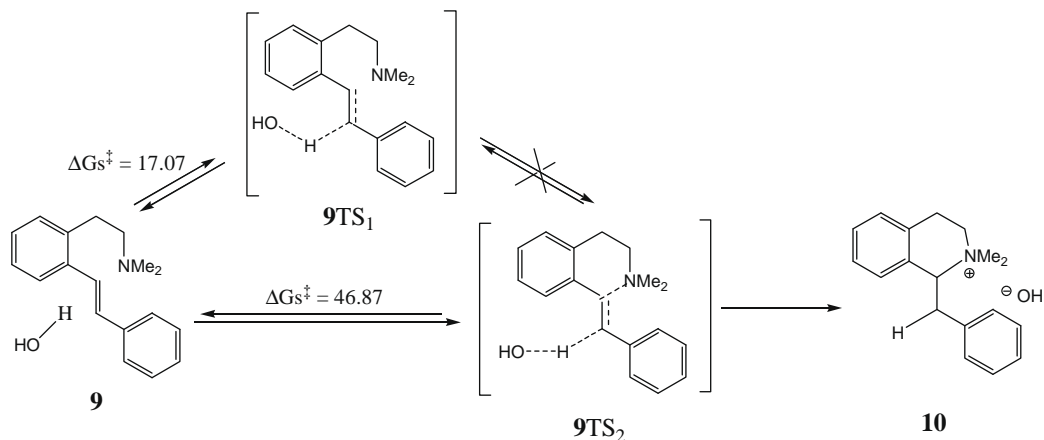
HF, B3LYP, and MM2 refer to values calculated using HF/6-31G, B3LYP/6-31G (d,p), and Allinger's MM2 methods, respectively. ΔE_s is the MM2 difference in strain energies of the products and the reactants in kcal/mol. ΔH^\ddagger is the activation enthalpic energy (kcal/mol). $T\Delta S^\ddagger$ is the entropic energy in kcal/mol. ΔG^\ddagger is the activation free energy (kcal/mol).

Comparison of the activation energies (ΔG_s^\ddagger) for process **6** with that of **3** reveals that ΔG_s^\ddagger for the latter, as calculated by B3LYP/H₂O, is 20.85 kcal/mol higher than that for **6** (36.88 kcal/mol vs 17.64 kcal/mol). This discrepancy might be due to: (1) the approach of the proton from H₂O toward the carbon of the carbon-carbon double bond in **6** being much easier than that for the proton in **3** (16.03 kcal/mol vs 28.41 kcal/mol) due to stabilization of **6TS₂** by the benzene rings. (2) The product **7** (two six-membered fused rings) is less strained than the corresponding ten-membered ring reactant, ($E_s = 12.12$ kcal/mol vs $E_s = 15.19$ kcal/mol), whereas in the case of **3** the strain energy of the product is about 11.52 kcal/mol higher than that of the reactant ($E_s = 36.93$ kcal/mol vs 25.41 kcal/mol, see Table 2) and, (3) the distance between the two reactive centers (N and C of the double bond) in **6** is shorter than the same distance in **3** (C–N = 3.18 Å vs 4.50 Å, see Fig. 1).

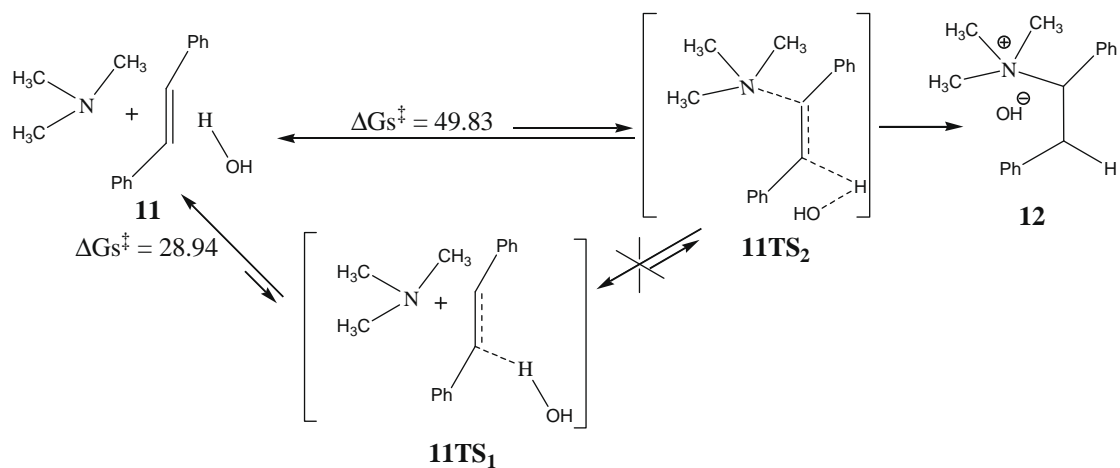
In order to examine the contribution of the benzene rings on the stability of the transition states in the addition reaction of **6**, DFT calculations for ring-closing of **9** as shown in Scheme 4 were performed. The results reveal that the calculated activation energy for this process is much higher than that for process **6** (46.87 kcal/mol vs 17.64 kcal/mol) and that for process **3** (46.87 kcal/mol vs 36.88 kcal/mol). Since the reactant **9** has similar chemical groups as **6** with the exception of the C–N distance in **9** being much longer than that in **6** (4.51 Å vs 3.18 Å) due to strain effects imposed as a result of the involvement of a ten-membered ring, the discrepancy

in the activation energies for the two processes is due to proximity orientation effects. To examine how far the presence of the adjacent amine nitrogen favors the 'almost incredible' proton transfer from water to the stilbene C–C double bond, the DFT calculated values for the distance between the amine nitrogen and the carbon of the double bond (C–N) for processes **3**, **6**, **9**, and **11** (Scheme 5) were compared against the corresponding calculated activation energies (Table 3). Examination of Table 3 reveals that significant rate acceleration (low activation energy) is achieved when the C–N bond distance is about 3.18 Å. This 'critical distance' could be achieved in processes where the reactant is much more strained than the corresponding product. Consequently, juxtaposition of the two reactive groups leads to a rapid addition of the amine to the carbon-carbon double bond. Although the first transition state for process **9** is stabilized by the benzylic ring, the activation energy for **3** is much lower than that of **9** due to proximity orientation (C–N for **3** is 3.93 Å vs 4.51 Å for **9**). To further quantify the effect of the C–N distance on the addition reaction rate, linear correlation of the DFT-calculated energy (ΔG_s^\ddagger) with the C–N distance ($1/r$) was examined. The results depicted in Figure 2 indicate a relatively good correlation between the two parameters with a correlation coefficient, $R = 0.96$. Thus, systems having short C–N distances exhibit low activation energy (high rate) and vice versa.

It is worth noting that the DFT calculation results indicate that the reverse Hofmann elimination mechanism (protonation of the



Scheme 4. Intramolecular addition of **9** in the presence of water to furnish tetraalkylammonium hydroxide **10**. The activation energy values are in kcal/mol.



Scheme 5. Intermolecular addition of trimethylamine to *trans*-stilbene in the presence of water to furnish tetraalkylammonium hydroxide **12**. The activation energy values are in kcal/mol.

Table 3
DFT calculated C–N bond distance and activation energy for the nucleophilic addition reactions in **3**, **6**, **9**, and **11**

System	C–N distance (Å)	ΔG_1^\ddagger (kcal/mol)	ΔG_2^\ddagger (kcal/mol)	ΔG_T^\ddagger (kcal/mol)
3	4.50	28.41	8.47	36.88
6	3.18	16.03	1.61	17.64
9	4.51	26.04	20.83	46.87
11	5.98	39.50	12.66	52.16

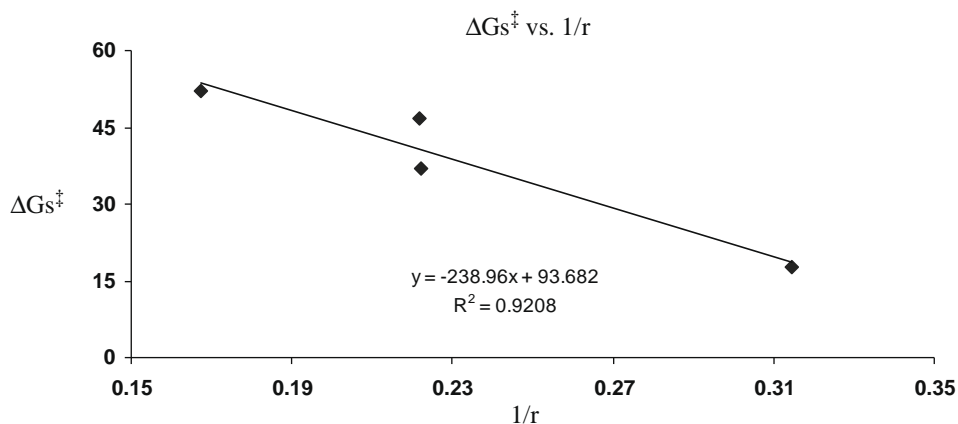


Figure 2. Plot of the DFT-calculated free activation energy (ΔG_s^\ddagger) in water as a solvent versus calculated $1/r$ values for systems **3**, **6**, **9**, and **11**. r is the DFT-calculated C–N distance in the global minimum structure (GM).

double bond to form a carbonium ion followed by an attack of the amine nitrogen) is not feasible in the case of processes **3**, **6**, and **9**, since the corresponding carbocations are relatively unstable (more so than TS1 and TS2 in the concerted mechanism).

The combined results suggest a concerted mechanism which involves nucleophilic addition of the amine nitrogen to the olefinic double bond, concerted with protonation by a molecule of water. Significant rate enhancements are observed in cases where substantial ground state strain is relieved on cyclization such as in the case of process **6**.

Intramolecularity is quantified by the 'effective molarity' (EM) parameter. EM is defined as $k_{\text{intra}}/k_{\text{inter}}$ for the corresponding intramolecular and intermolecular processes driven by identical mechanisms. Kirby's report of EM values indicates that they can range from less than 0.3 M to more than 10^{10} M and that they are affected by the ring size, solvent and reaction type.¹¹

The EM value for the unprecedented reaction of **6** is not available since the rate of the corresponding intermolecular process is extremely slow.³ In order to assess the effects of the structural features in **6**, we have calculated the corresponding intermolecular process, **11** to **12**, using both HF and DFT methods. Scheme 5 illustrates the mechanistic pathway by which trimethylamine interacts with *trans*-stilbene **11** in the presence of water, to yield tetraalkylammonium hydroxide **12**.

The results revealed that reaction of **11** occurs via two steps similar to **3**, **6**, and **9** with the exception that there is no ring-closing. Further, they indicate that the activation energy, as calculated by B3LYP/6-31G (d,p), is 52.16 kcal/mol (Scheme 5 and Table 2).

Using Eqs 3–7, we have calculated the EM values for processes **3**, **6**, and **9**: $\mathbf{3} = 1.6 \times 10^{11}$ M; $\mathbf{6} = 1.54 \times 10^{25}$ M; $\mathbf{9} = 7.33 \times 10^3$

$$EM = k_{\text{intra}}/k_{\text{inter}} \quad (3)$$

$$\Delta G_{\text{inter}}^{\ddagger} = -RT \ln k_{\text{inter}} \quad (4)$$

$$\Delta G_{\text{intra}}^{\ddagger} = -RT \ln k_{\text{intra}} \quad (5)$$

$$\Delta G_{\text{intra}}^{\ddagger} - \Delta G_{\text{inter}}^{\ddagger} = -RT \ln k_{\text{intra}}/k_{\text{inter}} \quad (6)$$

$$\Delta G_{\text{intra}}^{\ddagger} - \Delta G_{\text{inter}}^{\ddagger} = -RT \ln EM \quad (7)$$

where T is the temperature in Kelvin and R is the gas constant. The calculated EM value for **6** is extremely high and is comparable to the rate of a reaction catalyzed by the most efficient enzyme discovered to date.¹

In summary, the reaction mechanism of Kirby's amine olefin **6** is concerted: proton transfer from a molecule of water onto the carbon–carbon double bond concerted with nucleophilic attack of the amine nitrogen onto the other carbon of the carbon–carbon double bond. Comparison of the reaction of **6** to those of **3** and **9** reveals that the activation energy for process **6** is much less than that for either of the other two processes (**3** and **9**) because of the lower energy needed to overcome the barrier for ring-closing in the second step. The discrepancy in the values of the energy barriers in **6** to those in **3** and **9** is attributed to ground state energy effects. The steric (strain) energy for the product in **6** is much smaller than that for the reactant whereas in the case of **3** and **9**, the steric energy of the product is much higher than that of the reactant.¹² Another reason for this discrepancy might be the proximity orientation of the nucleophile and the electrophile. In system **6**, the distance between the two reactive centers is much smaller than the same distance in **3** and **9** due to the strain imposed on **6** as a result of the involvement of a ten-membered ring. EM calculations for processes **3** and **6** reveal that the latter undergoes the ring-closing reaction at a rate comparable to the rates for reactions catalyzed by the most efficient enzymes.

It is tempting to extrapolate our results to enzymes. Accordingly, we propose that enzymes achieve their remarkable catalytic activity

by imposing a range of contact distances within hydrophobic pockets at the active site. These contact distances and space create a strained status for the substrate–enzyme complex which triggers the latter to undergo cleavage to yield a less strained product.⁶

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Supplementary data

Calculation methods, Xyz Cartesian coordinates for the calculated GM and TS optimized structures in processes **3**, **6**, and **9** are available. Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.048.

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