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# Nornicotine Aqueous Aldol Reactions: Synthetic and Theoretical Investigations into the Origins of Catalysis

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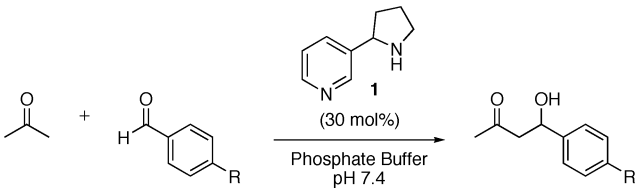
The recent discovery that nornicotine **1**, a minor nicotine metabolite, can catalyze the aldol reaction under physiologically relevant conditions has initiated research efforts into the potential chemical roles of nicotine metabolites. Herein, we disclose studies aimed at determining the origin and thus mechanism of the nornicotine-catalyzed aqueous aldol reaction. Conformationally constrained compounds designed to mimic the low-energy conformations of nornicotine were synthesized and tested for aldol catalysis; however, none showed rate enhancements on par with nornicotine. To further explore the mechanism of this process, a density functional theory (DFT) study was performed by using a variety of compounds previously tested for catalysis. These in silico studies have uncovered an unprecedented mechanistic subtlety of aqueous aldol reactions. Unlike the single transition state model observed for aldol reactions in organic solvent, the nornicotine-catalyzed reaction in water proceeds via a two-step mechanism in which a water molecule is utilized in both steps and a stable intermediate is generated. In total, these studies validate the proposed enamine-based mechanism of nornicotine-catalyzed aqueous aldol reactions and also provide the basis for future studies into the stereoelectronic nature of individual catalyst structures.

## Introduction

Cigarette smoking, the leading preventable cause of death in the United States,[1] is widely recognized to contribute to various ailments including coronary heart disease, stroke, vascular disease, peptic ulcers, chronic lung diseases and lung cancer, and fetal brain damage and morbidity. Despite these well-documented findings, a considerable percentage of the population continues to use commercially available tobacco products such as cigarettes, cigars, pipe tobacco, and snuff. Therefore, it is imperative to further explore the basis of the physiological consequences of tobacco use, including the specific contributions of its various molecular components.

Nornicotine **1** is a minor metabolite of nicotine and is also present naturally in tobacco via a demethylation process presumably involving cytochrome P-450.[2] It has been shown that nornicotine binds to the nicotinic acetylcholine receptor (nAChR) with approximately one-third of the affinity of its parent compound,[3] and furthermore, it is the only nicotine metabolite to possess psychoactive properties.[4] Additionally, nornicotine, in vivo, has a plasma half-life of 8 h, significantly longer than that of its parent compound, nicotine (half-life ≈ 1 h). This extended half-life, in conjunction with the known reactivity of secondary amines, led us to initiate a program into the study of the chemistry of nornicotine in vivo.

**SCHEME 1. Catalysis of the Aldol Reaction by Nornicotine under Aqueous Conditions. (R = $NO_2$, Cl)**




The capacity of nornicotine to perform chemistry in water via an iminium ion-based mechanism is unprecedented. However, we have recently discovered that nornicotine is capable of serving as a catalyst for aldol reactions under buffered aqueous conditions[5] (Scheme 1). Additional credence for our hypothesis that nornicotine-based iminium ions can form in vivo has been shown in

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(1) (a) Nelson, D. E.; Kirkendall, R. S.; Lawton, R. L.; Chrismon, J. H.; Merritt, R. K.; Arday, D. A.; Giovino, G. A. *Morbid. Mortal. Wkly. Rep.* **1994**, *43*, 1−8. (b) U.S. Department Health and Human Services *Reducing the health consequences of smoking. 25 years of progress. A Report of the Surgeon General*; Public Health Services: Rockville, MD, 1989.

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(3) Teng, L. H.; Crooks, P. A.; Buxton, S. T.; Dwoskin, L. P. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 778−787.

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the aberrant glycation of proteins leading to the formation of a nornicotine-derived advanced glycation endproduct (AGE).[6] Further reports into this process have also revealed the ability of the nornicotine-derived AGE to inhibit the aggregation of the amyloid $\beta$-protein.[7] Interestingly, prior to these studies there were no reported examples of any metabolite that is able to catalyze a chemical reaction pathway. As such, we have begun to unravel the mechanism of this fascinating process and it appears the aqueous nornicotine-catalyzed aldol reaction proceeds through a transient enamine nucleophile. Finally, although nornicotine was found to be an efficient catalyst for the aqueous aldol reaction, other compounds containing similar functionality (e.g., proline, pyrrolidine) were not competent catalysts.

## Results and Discussion

**Role of Conformational Constraint in Catalyst Activity.** To investigate the underlying principles behind this intriguing chemical reaction, we undertook a study to determine which features of the catalyst were critical to obtain optimal rate enhancement. Our initial studies showed that an aromatic moiety coupled to the pyrrolidine nucleus was critical for optimal catalysis;[5] however, the catalytically active conformation of nornicotine in this mechanism was not readily apparent. Previous computational and spectroscopic studies have demonstrated that the most stable conformers of nicotine[8] and nornicotine[9] have the pyridine and pyrrolidine rings placed roughly perpendicular to each other. Two rotamers exist which satisfy this requirement, with the conformation placing the two nitrogen atoms on opposite sides of the molecule being consistently favored in both the gas phase and water by various computational techniques.[8] By constraining nornicotine into one of these two conformations, catalysis could be enhanced, provided that one of these two conformers is the preferred orientation in catalysis of the aldol reaction.

Recently, a significant resurgence in the development of constrained analogues of nicotine specific for the nAChR has occurred, primarily due to the discovery that nicotine possesses properties potentially conducive to the treatment of a variety of disorders including Alzheimer's disease, anxiety, adult attention deficit hyperactivity disorder, depression, Parkinson's disease, schizophrenia, Tourette's syndrome, and ulcerative cholitis.[10] Although attempts to unequivocally identify a definitive pharmacophore have been met with mixed success, a number of compounds have been prepared which are capable of specifically activating nAChRs (Figure 1). Of particular interest to our studies were isomeric constrained nicotine

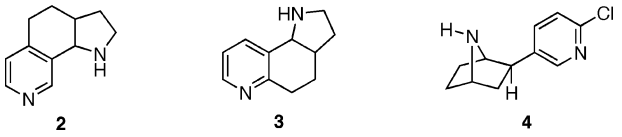
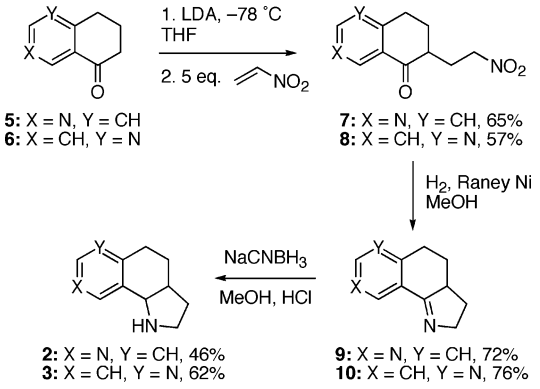



**FIGURE 1.** Representative nicotine analogues.

**SCHEME 2. Synthesis of Constrained Nornicotine Analogues 2 and 3**




analogues **2** and **3** and the natural product epibatidine **4**. These compounds closely resemble **1** in structure and preserve both the critical pyridine and pyrrolidine functionalities.

The two isomers **2** and **3** were synthesized as previously reported with slightly modified procedures.[11] Michael addition of nitroethylene to dihydroquinolones **5** and **6** followed by hydrogenation of the resulting nitroketones **7** and **8** yielded Schiff bases **9** and **10** in good yield. Reduction with sodium cyanoborohydride afforded constrained nornicotine analogues **2** and **3** in 22% and 27% yield over three steps, respectively. To ascertain the ability of each compound to serve as an aqueous aldol catalyst, the formation of the aldol addition product between acetone and 4-nitrobenzaldehyde was monitored by reversed-phase high performance liquid chromatography (RP-HPLC). The reaction was performed under pseudo-first-order conditions with previously reported conditions.[5] Interestingly, neither of the constrained nornicotine analogues was able to catalyze the aldol reaction as efficiently as nornicotine (Table 1).

Other constrained nornicotine analogues, such as epibatidine **4**, showed no rate enhancement over background rates, demonstrating that simple constraint of the nornicotine alkaloid motif is not sufficient for catalysis. An unconstrained compound containing both pyridine and amine functionalities, 3-aminomethylpyridine **11**, also did not catalyze the aldol reaction over background rates. In total, these results further confirm our previous findings that the stereoelectronic character of an aromatic ring, and pyridine in particular, is critical in obtaining observable rate enhancement.

**Computational Studies.** To better understand the underlying mechanism behind this chemical reaction, we have carried out a theoretical investigation of the nornicotine-catalyzed aldol reaction along with a number of other nornicotine analogues using density functional

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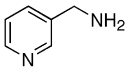
**TABLE 1. Pseudo-First-Order Rate Constants for the Reaction of Acetone with 4-Nitrobenzaldehyde in the Presence of Amine Catalysts (30 mol %) in Phosphate Buffer**[a]

| Entry | Catalyst | $k_{obs}$ ($min^{-1}$) |
|---|---|---|
| 1[b] | **1** | $10.1 \times 10^{-3}$ |
| 2 | **2** | $3.3 \times 10^{-3}$ |
| 3 | **3** | $1.9 \times 10^{-3}$ |
| 4 |  **11** | $1.0 \times 10^{-3}$ |
| 5 | **4** | $0.8 \times 10^{-3}$ |
| 6[b] | Uncatalyzed reaction | $0.7 \times 10^{-3}$ |

[a] Kinetic assays were performed in aqueous buffer (200 mM sodium phosphate, pH 8.0) at 37 °C with 10% DMSO to enhance substrate solubility. The reaction was followed by monitoring generation of the aldol addition product by reversed-phase HPLC. The assay was started by addition of aldehyde (1−8 mM in DMSO) to a mixture of the catalyst (2.4 mM) and acetone (240 mM) in the aqueous buffer system. Rate constants were calculated by using linear regression analysis. [b] See ref 5.

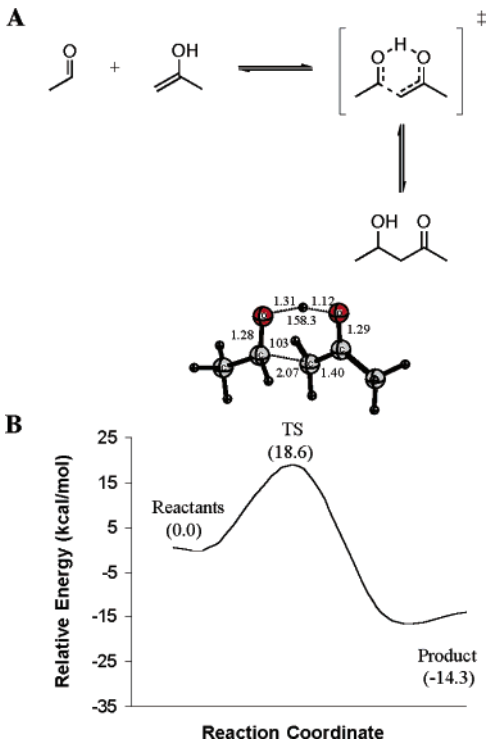



**FIGURE 2.** (A) Mechanism of the model aldol reaction of acetone and acetaldehyde in THF. (B) Calculated reaction coordinate and transition state structure for the model aldol reaction in THF. Bond lengths are shown in angstroms. Bond angles are shown in degrees.

theory. This study also provides critical insight into the nature of this reaction, and thereby, should allow for a clear understanding of aqueous amine catalysis as well as the future identification of other aqueous organocatalysts operating by an enamine mechanism. In our computational studies, this seemingly intricate reaction is also compared to a more simple aldol reaction both in THF and in water, whereby the latter reaction is also known to act as a reference background for the observed rate of reaction.

**Simple Aldol Reaction in Organic Solvent.** Aldol reactions in organic solvents are well documented and known to proceed through a well-defined reaction pathway in which the rate-determining step is the formation of the C−C bond between the enol and the aldehyde.[12] To model the basic reaction, we used the simplest reactants, acetone and acetaldehyde, but the obtained results should have general and widespread applicability for aldol reactions in organic media.

The results of our calculations show that this simple reaction proceeds through a single concerted transition state, in which C−C bond formation is concurrent with proton transfer from the enol to the aldehyde to yield the aldol product with an activation barrier of 18.6 kcal/mol (Figure 2A). This value is consistent with those expected for aldol reactions occurring spontaneously at room temperature and gave us confidence that our theoretical approach models aldol reactions in a reliable fashion. The reaction is exothermic, with the aldol product being −14.3 kcal/mol lower in energy that the initial reacting species.

**Aldol Reaction in Aqueous Media.** As a preface to understanding the nornicotine-catalyzed reaction by analogy, we have also examined this simple reaction scheme in an aqueous environment. There are significant differences between the simple reaction performed in organic solvent and the corresponding aqueous reaction, the most striking being that the experimentally observed reaction rate is much slower in the latter. Proposing mechanistic schemes that might explain such differences in reactions can be a difficult challenge, especially when one considers that mechanistic details of aldol reactions in aqua employing enamine intermediates are not well documented.

We propose that aqueous aldol reactions proceed through a stepwise, rather than concerted mechanism (Figure 3A), with the initial set of reacting species requiring two explicit water molecules that act as a proton donor or acceptor. Interestingly, we found that two explicit water molecules are necessary as one water molecule is not sufficient to form the product and regenerate water in the simple stepwise catalytic reaction. Furthermore, the barrier to formation of the second transition state is exceedingly high (>30 kcal/mol) due to the presence of a four-membered ring. Three water molecules were also employed in an attempt to further lower the barrier to the formation of the second transition state (from 15 kcal/mol), but even with the added complexity of a third water molecule incorporated into the calculations, no further lowering of the barrier was achieved. In the first step of the reaction, one of the water molecules completes the ring of a six-membered transition state, TS1, shown in Figure 3B, in which C−C bond formation, proton transfer from water to acetaldehyde, and C−OH bond formation occur simultaneously. Following this step, TS1 collapses to form a stable, yet short-

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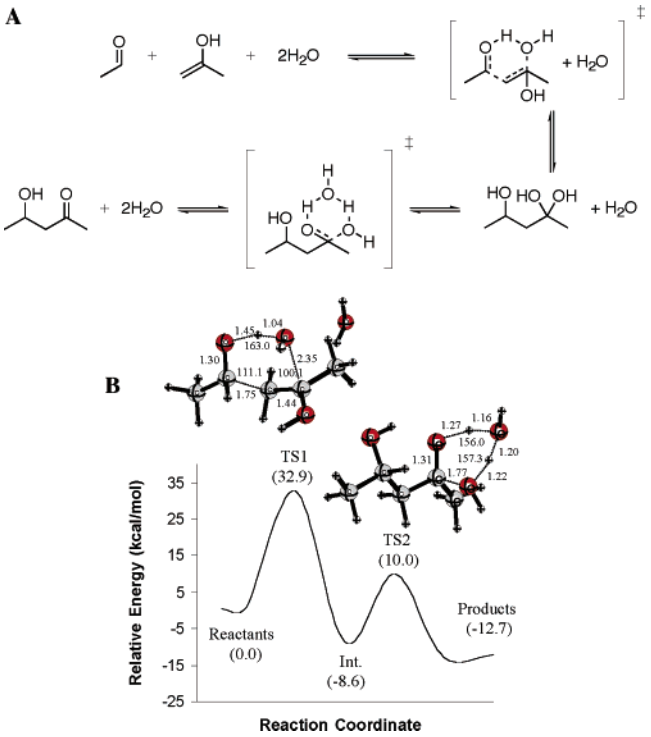


**FIGURE 3.** (A) Proposed mechanism of uncatalyzed aqueous aldol reaction. (B) Calculated reaction coordinate of uncatalyzed aldol reaction in water. Bond lengths are shown in angstroms. Bond angles are shown in degrees.

lived $\beta$-hydroxy-geminal diol intermediate. The barrier to formation of TS1 is 32.9 kcal/mol and the reaction is exothermic by 8.6 kcal/mol.

Subsequently, in the second and final step of the reaction, a second water molecule then completes the ring of another six-membered transition state, TS2 (Figure 3B). In TS2, the role of this second water molecule is to promote cleavage of the C−OH bond via proton donation, while it regenerates itself by accepting a proton from the neighboring hydroxyl group. TS2 then collapses to yield the aldol product and the explicit water molecules noted in the starting reactants become regenerated. Formally, each step of the mechanism is catalyzed by a water molecule, a phenomenon that has previously been observed in other reaction systems.[13] The barrier to formation of TS2 is 18.6 kcal/mol relative to the intermediate and the second step in the reaction is exothermic by 4.1 kcal/mol. Overall, the rate-determining step can be correlated with the largest barrier associated with the reaction profile as seen in TS1, where C−C bond formation, proton transfer from the water to acetaldehyde, and C−OH bond formation occur simultaneously to form the intermediate.

In both the aqueous aldol reaction and the aldol reaction in organic solvent, the rate-determining step is formation of the C−C bond coupled with proton transfer, yet the barrier to reaction in water is higher by 14.3 kcal/mol. Typically, spontaneous reactions at room temperature only occur when the barrier heights range between 18 (enzymes) and 25 kcal/mol (test tubes). The calculated barrier of approximately 30 kcal/mol is, in this respect, rather large. However, it may arise as a result of errors in the density functional methodology employed as there are error bars of 2−3 kcal/mol that can be associated with all calculated stationary point and transition state structures along the reaction coordinate. There is also the possibility that the mechanism we have proposed is one of several and the one we have presented here may not have the lowest barrier. Nonetheless, the calculated trend is correct: the reaction in water is predicted to be slower than the reaction in organic solvent by several orders of magnitude.

**Aqueous Nornicotine-Catalyzed Aldol Reactions.** Nicotine exists in both cis and trans rotamers about the bond connecting the two rings, and taking into account the relative orientation of the pyridine ring and *N*-methyl group, there are four possible conformers. These conformers were noted in previous reports, and the trans rotamers, in which the pyridine ring and *N*-methyl group are on opposite sides of the pyrrolidine ring, are favored over the corresponding cis alternatives.[8] Furthermore, our studies have confirmed that the rotamer in which the pyridine and pyrrolidine nitrogens are as far apart as possible is also favored over the opposite conformation by approximately 1 kcal/mol. As such, our studies have only focused on the trans rotamer of nornicotine in which the two nitrogen atoms are placed on opposite sides of the molecule.

In proposing the reaction pathway catalyzed by nornicotine and its homologues, we have assumed that the reaction proceeds through a well-defined enamine-driven mechanism, similar to that for the simple aldol reaction in water (vide supra). Thus, in our computational studies, the enamine is preformed from the condensation of acetone with nornicotine prior to the start of the calculations. Although this assumption does not include the possibility of hydrolysis of the nornicotine enamine by adventitious water, the demonstration of the presence of a nornicotine-derived enamine in aqueous buffer has been previously verified by using NMR techniques.[5] Furthermore, although the major protonation state of nornicotine in aqueous buffer is monoprotonation on the pyrrolidine nitrogen,[8,9] in order to invoke an enamine mechanism, the pyrrolidine nitrogen cannot be protonated and as such, we have not considered this equilibrium in our experiments.

As expected, the results of the calculations showed the major reaction product of the nornicotine condensation reaction to be the trans rotamer, again being more stable than its cis counterpart by approximately 1 kcal/mol. This trans conformation represents the starting point for the nornicotine-catalyzed reaction in water. The sequence of reactions begins with the nornicotine-derived enamine, at least two water molecules, and 4-chlorobenzaldehyde as an aldehyde acceptor (Figure 4A). The *p*-chloro substituent was chosen as it is a suitable electron-withdrawing group electrophile for the nornicotine-catalyzed aldol reaction[5] while being operationally simpler to implement in the DFT calculations than the more electron-withdrawing nitro group. In the first step of the reaction, one of the water molecules completes the ring of a six-membered transition state, TS1′, in which C−C bond formation, proton transfer from the water to acetaldehyde, and C−OH bond formation occur simultaneously

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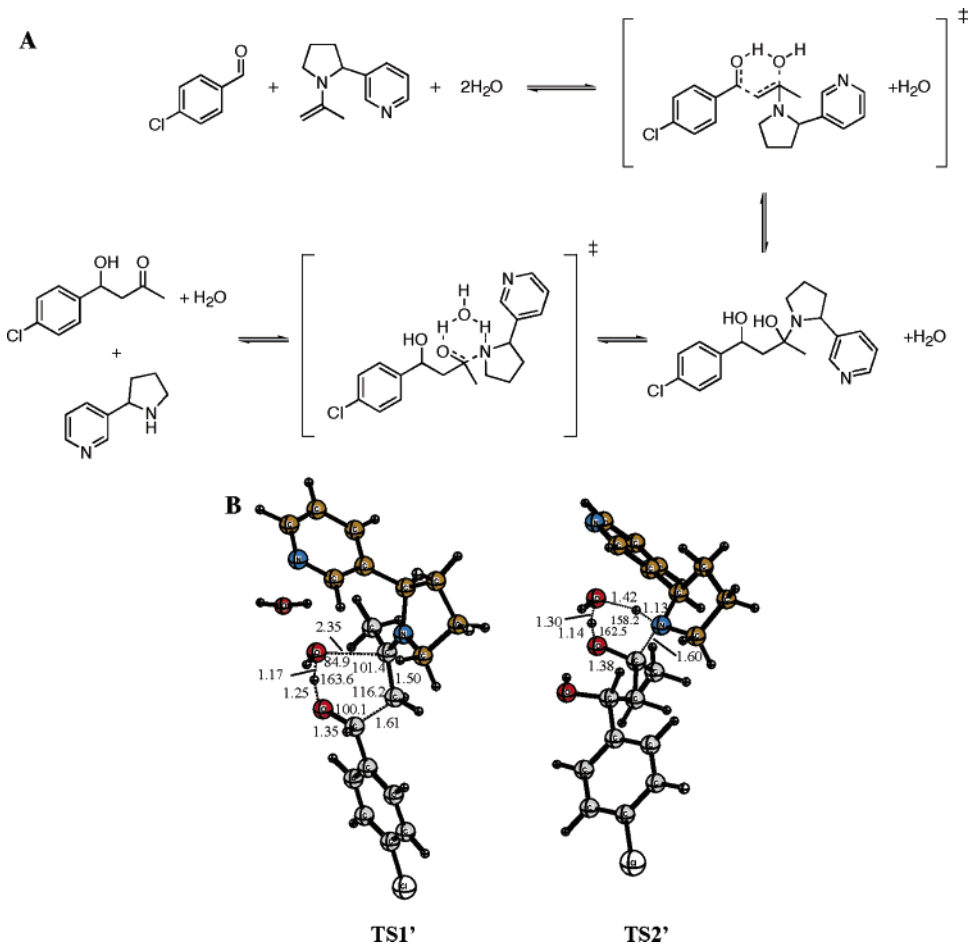


**FIGURE 4.** (A) Proposed mechanism for nornicotine-catalyzed aqueous aldol reaction. (B) Transition states calculated for the nornicotine-catalyzed aldol reaction between acetone and 4-chlorobenzaldehyde. Oxygen atoms are shown in red, nitrogen atoms in blue, carbon atoms from nornicotine in brown, and all other carbon atoms in gray. Bond lengths are shown in angstroms. Bond angles are shown in degrees.

(Figure 4B). As before, TS1′ collapses to form a stable yet short-lived $\beta$-hydroxy-hemiaminal intermediate species analogous to the $\beta$-hydroxy-geminal diol observed in the background reaction. The barrier to formation of TS1′ is 20.1 kcal/mol and the formation of the intermediate is endothermic by 8.0 kcal/mol. In the second and closing step of the reaction, a water molecule also completes the ring of another six-membered transition state, TS2′ (Figure 4B). In TS2′, the role of this second water molecule is to promote cleavage of the C−N bond via proton donation, while it regenerates itself by accepting a proton from the neighboring hydroxyl group. TS2′ then collapses to yield the aldol product that now includes one of the original explicitly defined water molecules while the other explicit water molecule noted in the starting reactants becomes regenerated, along with nornicotine; the second water molecule is regenerated in the enamine condensation. Both of the water molecules serve as catalysts in the mechanism, along with nornicotine. Gratifyingly, our data show that the nornicotine-derived enamine is significantly more nucleophilic in water than the corresponding enol, supporting known observations regarding enamines in organic synthesis.[14]

The energetics associated with the nornicotine-assisted reaction profile can be seen in Figure 5 in red. Formation of the C−C bond coupled to proton donation from the water and C−OH bond formation requires 20.1 kcal/mol while hydrolysis of the C−N bond in the second step only needs 15.3 kcal/mol and gives rise to an accumulated barrier to reaction of 23.3 kcal/mol. In this case, both initial C−C bond formation and final C−N bond hydrolysis contribute to the rate-determining step of the reaction, with the larger contribution from the former.

One of the key experimental observations that motivated the theoretical examination was that the rate of reaction was slowed by an order of magnitude (~1.4 kcal/mol) for the nornicotine derivatives. However, we note that 1.4 kcal/mol is a relatively small effect and to reliably predict such small differences in reactivity via a theoretical mechanistic investigation is very difficult. One must also consider that the inherent error associated with calculated structures is comparable to the observed rate acceleration.

We have performed similar calculations and identified similar transition states for the reactions of two other homologues of nornicotine, conformationally constrained

(14) (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222. (b) A noteworthy expection to this assumption can be found in the work of Reymond and co-workers. See: Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970−6979.

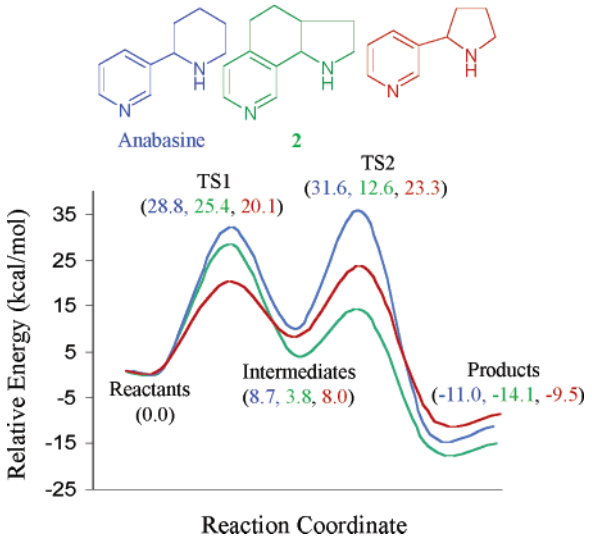


**FIGURE 5.** Reaction coordinate comparison of the catalysis of the aqueous aldol reaction by nornicotine (red), anabasine (blue), and conformationally constrained nornicotine analogue **2** (green).

analogue **2** and the minor nicotine metabolite anabasine, in which the pyrrolidine ring is replaced with a piperidine ring. The final energetics associated with these derivatives are also shown in Figure 5, in green and in blue, respectively. Barriers to reaction associated with corresponding structures are also given in the colored text matching that of the structure. Unfortunately, we were unable to employ this model to account for the observed differences in catalytic activity between 2- and 4-pyridyl-(2′-pyrrolidine) in comparison to nornicotine as the energy difference at the transition state (~1.4 kcal/mol) is not readily detectable and all compounds appear to have identical activity within experimental error.

In total, our computational data show that for the anabasine-catalyzed reaction, which has a reaction rate at or near the uncatalyzed rate, the initial barrier corresponds to 28.8 kcal/mol while the second hydrolysis step requires 22.9 kcal/mol, giving an accumulated barrier to reaction of 31.1 kcal/mol; for conformationally constrained structure **2**, 25.4 kcal/mol are needed for C−C bond formation while C−N bond breaking can be achieved with only 8.8 kcal/mol, suggesting again that the initial step is the major contributor and is rate determining. These reaction barriers, for anabasine, the rigid derivative, and nornicotine, at 31.1, 25.4, and 23.3 kcal/mol, respectively, suggest that nornicotine should be a better catalyst for the aldol reaction than the rigid structure by 1−2 orders of magnitude; it should also catalyze the reaction approximately 10−100 times faster than the uncatalyzed reaction. The calculated energy barriers for the catalyzed reactions are, at the extreme, 10 kcal/mol lower than the uncatalyzed anabasine reaction. Nornicotine should therefore also be a better catalyst than anabasine. Here though, it is important to note that the experimentally measured rates are only 1 order of magnitude faster in the nornicotine reaction. For reasons noted previously, the expected difference in barrier height of 1.4 kcal/mol can thus easily be exaggerated to values of around 6 kcal/mol (approaching 10 kcal/mol).

That these calculations do not reproduce the absolute rate differences observed experimentally, that is, 1 order of magnitude rate enhancement, is a concern but it is not surprising, given the small changes in the rate of reaction observed. In fact, to reproduce such small effects is in all likelihood beyond the current predictive capability of DFT. In further support of this point, we also performed calculations using 2-phenylpyrrolidine, a compound previously shown to catalyze the aldol reaction at a slightly slower rate than nornicotine;[5] no significant difference in the initial barriers was observed between nornicotine and 2-phenylpyrrolidine as the expected difference in energy is too small to be resolved by this method (data not shown).

While we acknowledge there is a clear discrepancy and lack of correspondence between our calculated absolute values for the barriers to reaction and the experimentally determined rates, this is an apparent shortcoming of the calculations. However, the most salient point to emerge is that the calculated trend in the accumulated barriers to reaction mimics the experimentally observed rates of reaction in a relative sense, suggestive that these calculations provide us with a realistic explanation for the origins for the nornicotine-catalyzed aldol reaction in water. Furthermore, these calculations support the experimental finding that the conformationally constrained nornicotine analogues **2** and **3** do not adequately mimic the catalytically active conformation of nicotine in the aqueous aldol reaction.

## Conclusion

A central tenet of studies toward "green" synthetic chemistry has been the development of catalytic reaction systems that function under mild, aqueous conditions. Although examples of enamine intermediates in aqueous environments have been shown, many assume that enamine-based catalysis and aqueous systems are inherently incompatible due to the rapid hydrolysis of the necessary enamine intermediates.[14b] Our recent demonstration that nornicotine, a minor nicotine metabolite, can catalyze aldol reactions in physiological buffer has challenged this notion, and has led us to closely examine the mechanism of this fascinating process using kinetic and computational techniques. In this study, we have tested a variety of constrained and unconstrained analogues of nornicotine in an effort to mimic the thermodynamically stable conformers of the alkaloid and increase the rate of catalysis. However, none of these compounds showed rate enhancements comparable to that of nornicotine. This disparity was confirmed through a DFT study of the nornicotine-catalyzed aldol reaction. Furthermore, our computational studies have also validated the proposed enamine-based mechanism of nornicotine catalysis and as well revealed an interesting mechanistic consequence of aqueous aldol reactions. In contrast to the single transition state of a model aldol reaction in organic solvent, both the catalyzed and uncatalyzed reactions appear to proceed through a two-step mechanism in water, in which a stable intermediate is generated. Although these studies do not elucidate the specific nature of nornicotine as a more efficient aqueous aldol catalyst relative to other tested compounds, a solid foundation is provided for further theoretical studies into

the stereoelectronic nature of individual catalyst structures, thereby guiding future synthetic efforts in the production of viable aqueous aldol catalysts.

## Experimental Section

**General Methods.** Unless otherwise stated, all reactions were performed under an inert atmosphere with dry reagents and solvents and flame-dried glassware. Analytical thin-layer chromatography (TLC) was performed with 0.25 mm precoated silica gel Kieselgel 60 $F_{254}$ plates. Visualization of the chromatogram was by UV absorbance, iodine, dinitrophenylhydrazine, ceric ammonium molybdate, ninhydrin, or potassium permanganate as appropriate. Preparative and semipreparative TLC was performed with Merck 1 mm or 0.5 mm coated silica gel Kieselgel 60 $F_{254}$ plates, respectively. Methylene chloride and chloroform were distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Methanol was distilled from magnesium. $^1$H and $^{13}$C NMR spectra were recorded at 500 and 125 MHz, respectively, unless otherwise noted.

**2,3,3a,4,5,9b-Hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline (2).** Nornicotine analogue **2** was prepared according to published procedures[11] with slight modifications: (a) the oxidation of tetrahydroisoquinoline was performed at elevated reaction temperatures (40 °C); (b) compounds were purified on silica with flash chromatography ($CHCl_3$:MeOH:$NH_4OH$ 85:15:1.5) in higher yields to those previously reported; and (c) the low yield of the Michael addition was improved by using multiple equivalents (4−5) of nitroethylene.

**2,3,3a,4,5,9b-Hexahydro-1*H*-pyrrolo[2,3-*f*]quinoline (3).** Nornicotine analogue **3** was prepared according to published procedures[11] with identical modifications as listed for the synthesis of **2**.

**Aqueous Aldol Reaction Screening.** The assay was initiated by the addition of a solution of 4-nitrobenzaldehyde (100 mM in DMSO) to a solution of acetone (240 mM) and catalyst (2.4 mM) in buffer (200 mM phosphate, pH 7.4). The total assay volume was 1 mL and the assay was performed at 37 °C. At times throughout the assay, aliquots (10 $\mu$L) were removed and diluted to a final volume of 0.5 mL with phosphate buffer. Aliquots of these diluted solutions (20 $\mu$L) were then removed and injected onto a RP-C18 HPLC column, equipped with a guard-column (HPLC conditions: isocratic mobile phase of acetonitrile:water (25:75) with 0.1% TFA; solvent flow rate of 1 mL min$^{-1}$ and detection at 254 nm). Aldol addition product formation (retention time = 6.2 min) was determined by interpolation of peak height and area values relative to standard curves.

**Rate Constant Determination.** The rate constant for each catalyst was determined by the method of initial rates under pseudo-first-order conditions. The assay was initiated by the addition of a solution of 4-nitrobenzaldehyde (1−8 mM) in DMSO to a solution of acetone (240 mM) and catalyst (2.4 mM) in buffer (200 mM phosphate, pH 8.0). The reaction was followed for no more than 5% of the reaction during which the rate was linear ($r^2 > 0.990$).

**Computational Studies.** All geometries and energies presented in the present study were computed by using the B3LYP density functional theory[15] method as implemented in the Gaussian98 program package.[16] Geometry optimizations were performed by using the triple-$\zeta$ plus polarization basis set 6-311G(d,p), followed by single point energy calculation with the larger basis set 6-311+G(2d,2p). Hessians were calculated at the HF/3-21G level of theory. Hessians provide a control that the stationary points localized are correct, with no imaginary frequencies for minima and one imaginary frequency for transition states, and also allow evaluation of the zero-point vibrational effects on energy. Electrostatic solvent effects were modeled with use of the conductor-like solvation model COSMO at the B3LYP/6-311G(d,p) level. In this model, a cavity around the system is surrounded by polarizable dielectric continuum.[17] The dielectric constant for the solvent is chosen to be $\epsilon = 80$, a widely accepted standard for water. To describe the simple aldol reaction in organic solvent, $\epsilon$ for THF was set at 7.6. All energies presented are enthalpies to which solvation energies are added. Zero-point effects are also included.

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