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Thermodynamic and kinetic factors in the aza-Cope rearrangement of a series of iminium cations

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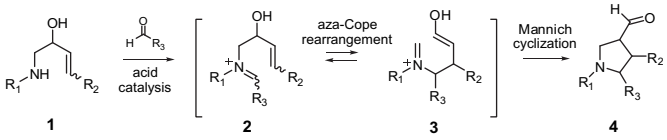
ABSTRACT

The effects of C–C bond conformation, double bond geometry, and relative stereochemistry on the kinetic and thermodynamic stability of 30 iminium cations as they undergo an aza-Cope rearrangement have been examined via density functional calculations for the purposes of predicting stereoselectivity in the reaction sequence. DFT predicted transition states were consistent with experimentally observed stereoselectivities. The calculations were then extended to the rearrangements of other iminium cations with varying substitution patterns to identify trends in rearrangement pathways. These trends should provide insight into controlling stereoselectivity in this reaction sequence.

1. Introduction

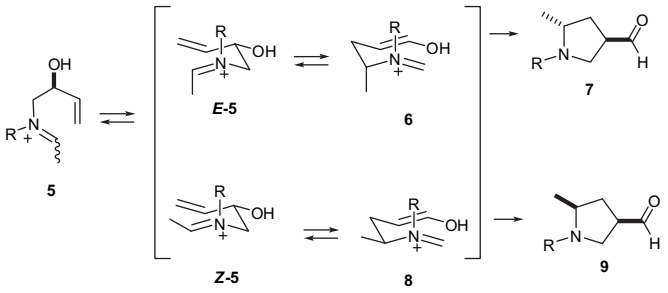
Tandem reactions[1] are a highly efficient mean for rapidly increasing molecular complexity in a single synthetic step. Pioneered by Overman,[2] the cationic aza-Cope rearrangement–Mannich cyclization is a tandem sequence that is characterized by the formation of a 3-acylpyrrolidine **4** from a homoallylic iminium cation containing an allylic alcohol **2** (Scheme 1).[3,4] Experimental evidence has demonstrated that the sequence proceeds through a [3,3]-sigmatropic rearrangement of the iminium cation **2** with subsequent cyclization of the resulting enol **3** onto the transposed iminium cation.[4a,b]



Scheme 1.

The efficiency with which the reaction sequence generates pyrrolidines and the high degree of stereocontrol that is generally obtained make the aza-Cope–Mannich reaction an attractive tool for synthetic chemists. Indeed, this reaction has been used as the key step in a number of alkaloid total syntheses.[5]

Because the aza-Cope rearrangement generally proceeds through a chair-like transition state, the stereoselectivity for a particular iminium cation translates to diastereoselectivity in the acylpyrrolidine products (Scheme 2).[4c] If the *E*-iminium cation *E*-**5** undergoes aza-Cope rearrangement and subsequent Mannich cyclization via iminium cation **6**, the result is *trans*-acylpyrrolidine **7**. By contrast, if iminium cation *Z*-**5** undergoes rearrangement to form iminium cation **8**, subsequent cyclization would lead to the cis-diastereomer **9**.



Scheme 2.

Another important consideration for the stereochemical outcome of this reaction sequence is chirality transfer from the iminium carbinol to the α-carbon of the acylpyrrolidine, the success of which depends upon the hydroxyl substituent in iminium cation **10** selectively adopting either an axial or equatorial position (Scheme 3). Beginning with the β-carbinol enantiomer of iminium cation **10**, rearrangement and cyclization via the equatorial hydroxyl conformation lead to β-acylpyrrolidine **12**. If the hydroxyl instead adopts an axial orientation, rearrangement and cyclization would lead to α-acylpyrrolidine **14**.

This work examines the relative energies of iminium cations before and after an aza-Cope rearrangement as well as the

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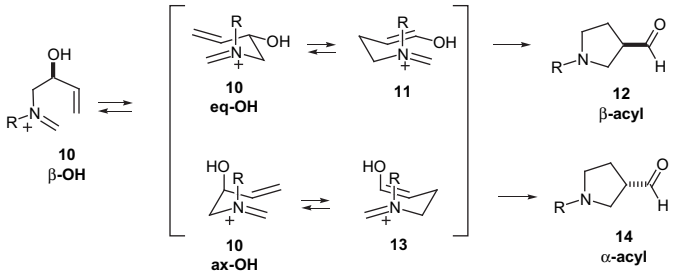
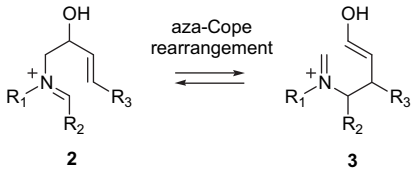


Scheme 3.

activation energy required for the rearrangement. Density functional calculations are used to compare iminium cation ground-state energies for axial versus equatorial hydroxyl groups and *E*- versus *Z*-iminium cation isomers before and after the aza-Cope rearrangement. In addition, relative kinetic stability is determined by calculating activation energies for the aza-Cope rearrangement. These comparisons are then extended to systems having either *E* or *Z* C–C double bonds, and ultimately applied to aza-Cope rearrangements of more substituted iminium cations. Because stereoselectivity depends upon an energetic advantage for one set of variables over others, we anticipate that this method may be useful for predicting selectivity, or lack thereof, in these reactions. The results shed light on which factors may affect the formation of a particular acylpyrrolidine stereoisomer.

2. Details of the calculations

The Gaussian 03 software package was used for all calculations.[6] Initial molecular structures were created using Gauss View 03 for Windows.[7] Geometry optimization calculations were carried out using density functional theory, specifically B3LYP/6-311+G(d,p) for the structures in Schemes 3 and 4 and B3LYP/6-31G(d,p) for the structures in Figure 5.[8,9] Each structure was optimized to either a minimum or a saddle point (transition states) using the Berny algorithm[10]; force constants and resulting vibrational frequencies were computed analytically. To ensure that the transition state structures were those for the appropriate pathway, an IRC calculation[11,12] was performed on the *E*-C–C double bond, *Z*-iminium cation, equatorial –OH isomer in Figure 5.



Scheme 4.

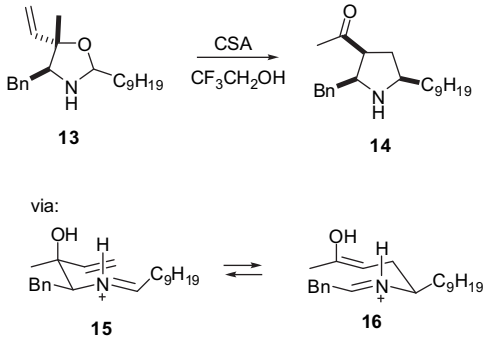
In addition, QST2 and QST3 calculations[13] were performed for all of the iminium cation isomers shown in Scheme 4, where R_1=H and R_2, R_3=H or CH_3.

To calculate relative activation energies for the structures shown in Schemes 6 and 8, model complexes were used to shorten the necessary computing time. In these model compounds, the Bn and C_9H_{19} groups were substituted with methyl groups.

3. Results and discussion

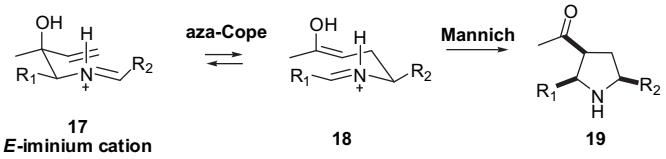
3.1. Theoretical and experimental comparison

Initially, in an effort to test the efficacy of the theory for correctly predicting the reaction pathway, we examine the aza-Cope rearrangement of iminium cations used in Overman's synthesis of (+)- and (−)-preussin.[4g] To install the pyrrolidine stereocenters, Overman employed a camphorsulfonic acid (CSA)-mediated aza-Cope–Mannich rearrangement of oxazolidine **13** that resulted in acetyl-pyrrolidine **14** as the major isomer (Scheme 5). The observed stereochemical outcome may be rationalized by the aza-Cope rearrangement of *E*-iminium cation **15** via the chair topography shown below (Scheme 5), followed by Mannich cyclization of rearranged iminium cation **16**.



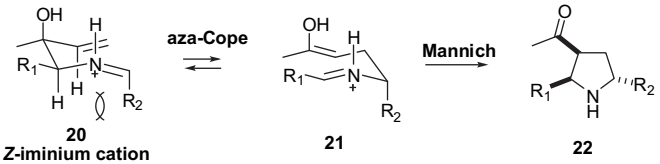
Scheme 5.

Accordingly, we performed calculations on the two iminium cation stereoisomers **17** and **20** that could be formed in Overman's experiment to determine whether computational results would support the rationalization for the stereochemical outcome of the reaction (Scheme 6). Because a pseudo-chair inversion would most certainly be higher in energy as it would place both the methyl and benzyl (R_1) substituents in pseudo-axial positions, only two of the four possible chair conformations were considered.[4g] The results indicate that the *E*-iminium cation **17** is more stable than the *Z*-



aza-Cope rearrangement of cation **17**
(relative energies in kcal/mol)

reactant	0.0	R_1,R_2 = CH_3
TS	14.6	R_1,R_2 = CH_3
E_a	14.6	R_1,R_2 = CH_3
ΔE	-2.9	R_1 = Bn, R_2 = C_9H_{19}



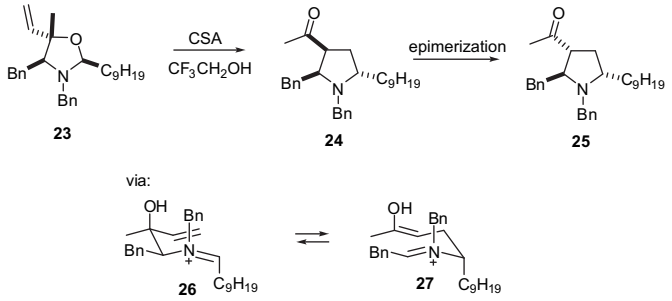
aza-Cope rearrangement of cation **20**
(relative energies in kcal/mol)

reactant	2.1	R_1,R_2 = CH_3
TS	17.3	R_1,R_2 = CH_3
E_a	15.2	R_1,R_2 = CH_3
ΔE	-9.6	R_1 = Bn, R_2 = C_9H_{19}

Scheme 6.

cation, likely because of allylic strain present in *Z*-cation **20**.[14] However, the aza-Cope reaction of the *Z*-cation is significantly more exergonic. Finally, the activation barrier for aza-Cope rearrangement of *E*-iminium cation **17** is somewhat lower than that for the *Z*-cation. Presumably the higher activation barrier for *Z*-cation **20** is due to developing pseudo-1,3-diaxial interactions in the transition state. At any rate, because *E*-cation **17** would form the experimentally observed[4g] acetyl-pyrrolidine **19** upon aza-Cope rearrangement and Mannich cyclization, these results suggest that the reaction is under kinetic control.

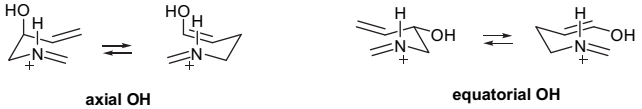
Overman also demonstrated experimentally that acetyl-pyrrolidine **25** could be formed as the major isomer by treating oxazolidine **23** with CSA (Scheme 7).[4g] Aza-Cope rearrangement of *Z*-iminium cation **26** followed by Mannich cyclization and subsequent epimerization would lead to the observed pyrrolidine stereochemistry **6**.



Scheme 7.

Calculations of the relevant iminium cations **28** and **32** (Scheme 8) indicate that *E*-iminium cation **28** is more thermodynamically stable, and that the aza-Cope rearrangement of *E*-iminium cation **28** is significantly more exergonic. Finally, and perhaps most importantly, the activation barrier for the rearrangement of *Z*-cation **31** is somewhat lower than that of *E*-cation **27** in spite of developing pseudo-1,3-diaxial interactions in the transition state. Because aza-Cope rearrangement via *Z*-cation **32** correctly predicts the experimentally observed stereochemical outcome,[4g] the calculations again suggest that the aza-Cope reaction is under kinetic control.

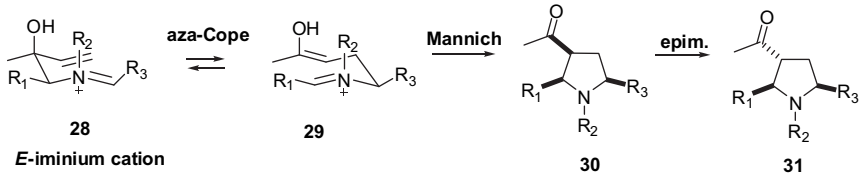
contribution of individual structural variables to the relative stability of the reactants, products, and transition states for the aza-Cope rearrangement of more conformationally mobile iminium cations. In the first set of calculations, we study the axial versus equatorial orientation of the allylic hydroxyl in iminium cations where neither the iminium cation nor the C–C double bond is substituted (Fig. 1).



	axial OH	equatorial OH
reactant	6.3	11.2
TS	18.0	20.2
product	0.0	2.7
E_a	11.7	9.0
ΔE	-6.3	-8.5

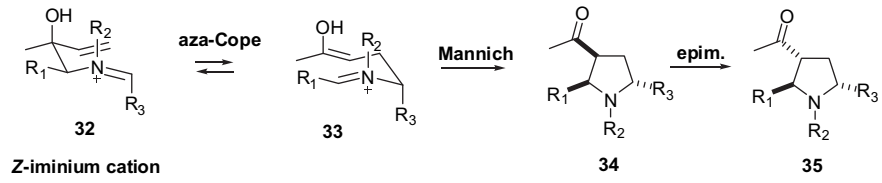
Figure 1. Relative total energies for reactants, transition states, and products for the aza-Cope reaction of iminium cations with either an axial or equatorial hydroxyl group. Energies are reported in kcal/mol.

The data indicate that when the hydroxyl substituent is equatorial the aza-Cope reaction is both thermodynamically and kinetically favored. However, the reactant with the hydroxyl in the axial orientation is more stable than the reactant where the hydroxyl is in the equatorial orientation, so that the former is expected to be more abundant in the reaction equilibrium mixture. The stability of the axial hydroxyl is due to hydrogen bonding between the iminium hydrogen and the hydroxyl group oxygen, as confirmed by the relatively short distance between these two atoms (3.12 Å) and the comparatively positive partial charge of the iminium hydrogen atom. Partial charges calculated from a Natural Bond Orbital analysis[15] show the iminium hydrogen as +0.46, while alkane hydrogens usually carry approximately a +0.2 charge. In addition, evidence of hydrogen bonding can be found in some of the occupied valence molecular orbitals, where there is significant electron density in the overlap region between the oxygen of the hydroxyl group and the hydrogen of the iminium nitrogen. Lastly, a Natural Bond Orbital analysis indicates that there is a donor–acceptor interaction between a lone pair on the oxygen center and the N–H σ* orbital. It should also be considered that a Curtin–Hammett[16] assumption that the rotational barrier between the axial –OH and equatorial –OH



aza-Cope rearrangement of cation **28**
(relative energies in kcal/mol)

reactant	0.0	$R_1,R_2,R_3 = CH_3$
TS	18.0	$R_1,R_2,R_3 = CH_3$
E_a	18.0	$R_1,R_2,R_3 = CH_3$
ΔE	-11.1	R_1,R_2 = Bn, $R_3 = C_9H_{19}$



aza-Cope rearrangement of cation **32**
(relative energies in kcal/mol)

reactant	2.6	$R_1,R_2,R_3 = CH_3$
TS	19.8	$R_1,R_2,R_3 = CH_3$
E_a	17.3	$R_1,R_2,R_3 = CH_3$
ΔE	-4.7	R_1,R_2 = Bn, $R_3 = C_9H_{19}$

Scheme 8.

3.2. Conformationally mobile iminium cations

Satisfied that our theoretical methods were appropriate for predicting the experimental reaction pathway for the aza-Cope rearrangement, we turn our attention to determining the conformers is less than either activation barrier would lead to the prediction that the aza-Cope reaction of the conformer having the equatorial hydroxyl group is the favored pathway.

In the next set of calculations we consider both the iminium cation geometry and the orientation of the hydroxyl substituent

(Fig. 2). By contrast to Overman's systems discussed above, all four of these iminium cations could, in principle, be accessible via a dynamic equilibrium. Consequently, all four aza-Cope pathways were compared. As was the case for the unsubstituted iminium cations (cf. Fig. 1), ground-state energies are lower for the axial –OH conformer in each pair, indicating their prevalence in the ground-state equilibrium mixture. However, for these substituted iminium cations, the reactions are endergonic because of hyperconjugation; specifically, there is a donor–acceptor interaction between two of the C–H σ bonds of the methyl group and the π* orbital of the double bond that stabilizes the reactant. Such interactions are not possible in either of the products where the iminium methyl substituent is allylic.

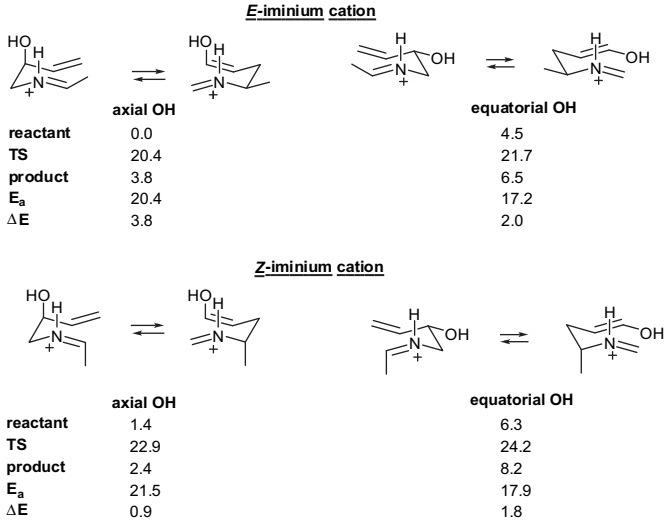


Figure 2. Relative total energies for reactants, transition states, and products for the aza-Cope reaction of *E*- or *Z*-iminium cations with either an axial or equatorial hydroxyl. Energies are reported in kcal/mol.

Of the four aza-Cope pathways, the activation barriers are significantly lower for the equatorial –OH iminium cations, results that are consistent with those for the unsubstituted iminium cations examined earlier. Interestingly, the iminium cation geometry has little effect on the activation barrier; the *Z*-iminium cation exhibits only a marginally greater activation energy than that of the *E*-cation for each pair of axial and equatorial hydroxyl rotamers. Of these aza-Cope rearrangements, the reaction via the *E*-iminium cation with axial –OH is the most kinetically favored. Finally, it is noteworthy that the activation energies for these rearrangements are higher than those of less substituted iminium cations (cf. Fig. 1).

For unsubstituted iminium cations with C–C double bond substitution, we find the reactions to be exergonic (Fig. 3). However, for all reactions but that of the iminium cation with a *Z*-C–C double bond and an axial –OH, the reactions are less exergonic than those of the simplest iminium cations (cf. Fig. 1), indicating a small but stabilizing effect imparted by the C–C double bond substituent. Presumably this stability results from hyperconjugation, but the effect is less significant than that observed for substituted iminium cations (cf. Fig. 2).

Consistent with other reactions, the activation barrier for the equatorial –OH rotamer is lower than for the axial –OH rotamer. Not surprisingly, the activation barrier for the iminium cation with *Z*-C–C double bond geometry is higher than for the analogous cation having *E*-C–C geometry, presumably owing to developing 1,3-diaxial interactions in the transition state. The activation barriers for these reactions were closer in energy to those of unsubstituted iminium cations than substituted ones, indicating that the

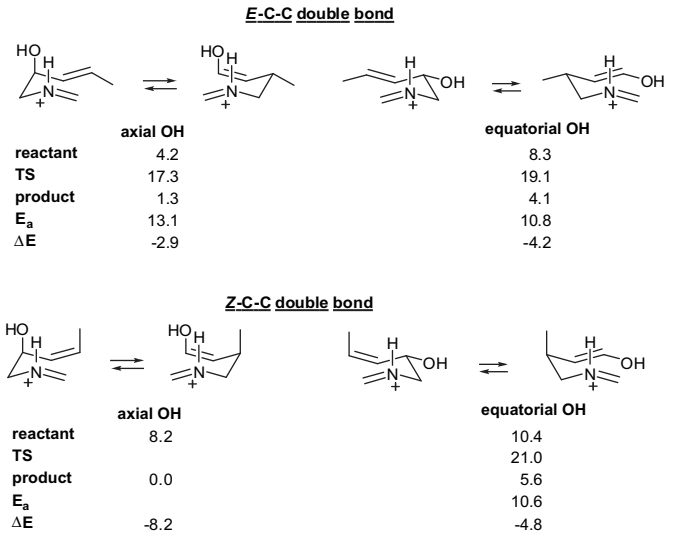


Figure 3. Relative total energies for reactants, transition states, and products for the aza-Cope reaction of iminium cations with either an axial or equatorial hydroxyl group and an *E*- or *Z*-C–C double bond. Energies are reported in kcal/mol.

effect of adding a C–C double bond substituent on the reaction rate is less significant than the addition of an iminium cation substituent. Unfortunately we were unable to locate a transition state for the iminium cation with an axial –OH and a *Z*-C–C double bond.

Finally we consider all three variables simultaneously (Fig. 4). For all pairs of C–C double bond isomers and iminium cation isomers, the axial –OH conformers have lower ground-state energy for both reactants and products, but the equatorial –OH conformers experience lower activation energies, a result that is consistent with all other conformationally mobile iminium cation pairs (cf. Figs. 1–3).

The activation energies for the equatorial –OH iminium cation having C–C double bond substitution are 2–9 kcal/mol (8–38 kJ/mol) greater than those for substituted iminium cations without C–C double bond substitution (cf. Fig. 2). This is not surprising, as additional developing pseudo-*gauche* butane and/or 1,3-diaxial interactions would be present when the additional methyl group is present as the C–C double bond substituent. Of the four possible iminium cations having an *E*-C–C double bond, the *E*-iminium cation with the equatorial –OH has the lowest aza-Cope activation barrier. For the iminium cations with *Z*-C–C double bond geometry, the iminium cation geometry has essentially no effect on the aza-Cope activation barriers. In these cases, the developing pseudo-*gauche* interactions in the *E*-iminium cation presumably balance the developing pseudo-1,3-diaxial interactions in the *Z*-isomer. Finally, in these reactions, all iminium cations having equatorial hydroxyl groups exhibit slightly lower activation energies than the iminium cations having an axial –OH.

For the sets of iminium cations in Figures 1–4, the calculations indicate that the aza-Cope activation energy significantly increases when an iminium cation substituent is added. By contrast, very modest activation energy increases are observed when a C–C double bond substituent is incorporated. In all cases, equatorial –OH conformers exhibit lower activation energies than the analogous axial –OH conformers.

3.3. Conformationally restricted iminium cations

Because of our experimental interest in rearrangements of pyrrolidine iminium cations, we next examine similar issues in a set of these more conformationally restricted molecules (Fig. 5). In

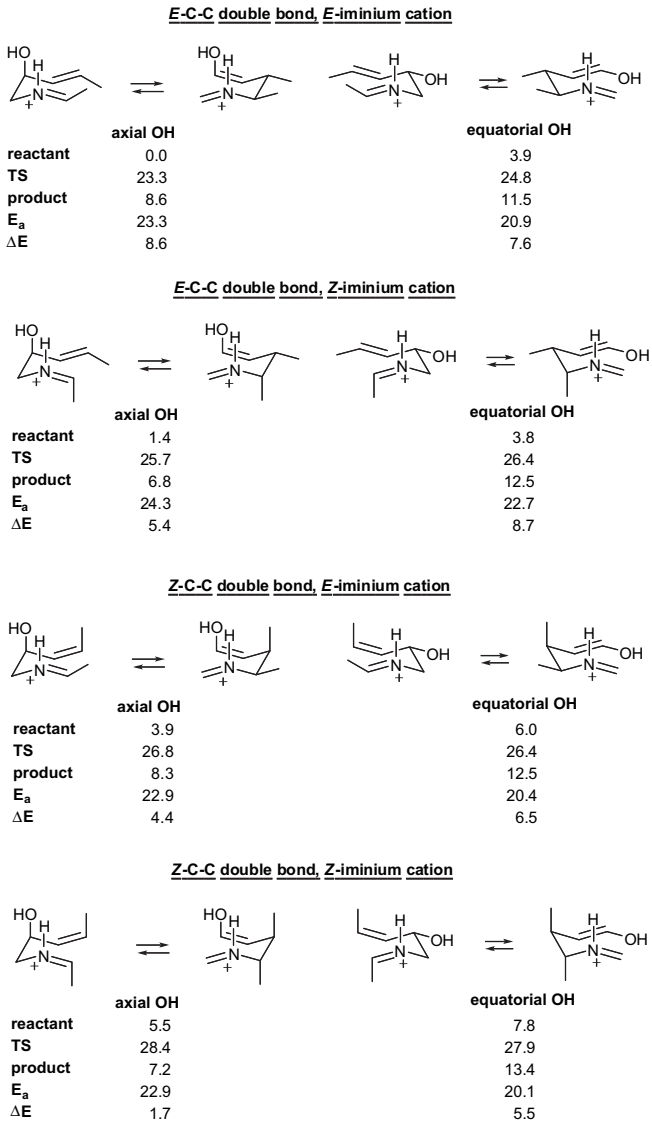


Figure 4. Relative total energies for reactants, transition states, and products for the aza-Cope reaction of iminium cations with either an axial or equatorial hydroxyl group and a methyl-substituted iminium cation and C–C double bond. Energies are reported in kcal/mol.

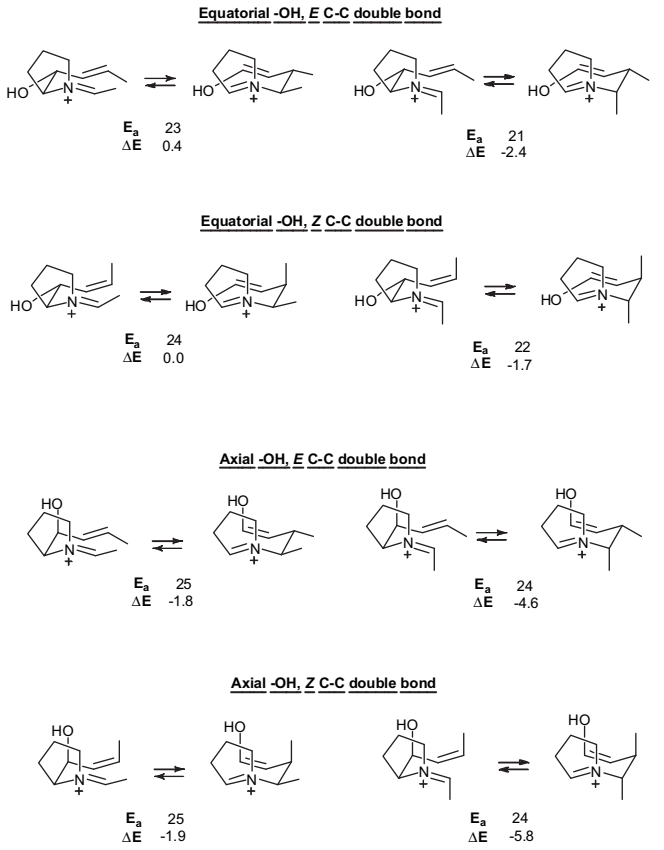


Figure 5. Activation energies and energies of reaction for all configurations of a pyrrolidine iminium cation.

these calculations, we choose not to examine axial and equatorial –OH conformational isomers because of the inability of these iminium cations to undergo a pseudo-chair inversion. Instead, we model pairs of iminium cation diastereomers where the hydroxyl could be either axial or equatorial.

The data indicate that all but one of the reactions is exergonic, which is consistent with the results of Overman's similarly substituted iminium cations (cf. Schemes 5–8). One explanation for this observation is that both the aza-Cope reactant and product iminium cations are stabilized by hyperconjugation; the reactant is stabilized by the methyl group, while the product is stabilized by the methylene of the cyclic iminium cation. As was the case for the conformationally mobile iminium cations, the equatorial –OH iminium cations have slightly lower activation energies. The effect of C–C double bond geometry on the activation barriers is negligible. Also consistent with aza-Cope reactions of substituted iminium cations with C–C double bond substitution (cf. Fig. 4), all activation energies range between 20 and 25 kcal/mol (85–100 kJ/mol). This is somewhat surprising; we expected that the pyrrolidine ring would introduce new developing 1,3-diaxial interactions in the transition state, causing higher activation energies than those observed for the iminium cation pairs in Figure 4. One explanation is that the additional steric instability is mitigated by the additional electronic (hyperconjugative) stability described above. While the differences in activation barriers are slight, in all cases the *Z*-iminium cation exhibits a lower activation energy for each pair.

4. Conclusions

Stereoselectivity in the aza-Cope rearrangement–Mannich cyclization may be affected at a number of points during this tandem sequence.[4d] For the purposes of this work, we have used DFT to examine the relative kinetic and thermodynamic stability of iminium cations that undergo the [3,3]-sigmatropic rearrangement portion of the sequence. Two trends emerge from the calculations. First, in all cases, lower activation barriers are observed for iminium cations having equatorial hydroxyls. This observation holds regardless of whether that conformer or stereoisomer is thermodynamically favored. Second, consistent with Overman's experimental results in more sterically biased systems,[4e] monosubstituted *E*-iminium cations are predicted to rearrange faster than the *Z*-isomers except in cases where rearrangement via the *Z*-cation circumvents a developing pseudo-*gauche* butane interaction. Significantly, for calculations involving the more substituted and conformationally rigid pyrrolidine iminium cation, determining the relative effects of iminium cation geometry and C–C double bond geometry on the reaction rates is not straightforward. Nonetheless, to the extent that the stereochemical outcome depends on the relative reactivity of iminium cation conformational isomers and/or iminium cation double bond isomers, we believe that these results

would be useful in predicting stereoselectivity in the aza-Cope–Mannich reaction.

Acknowledgements

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