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Ab Initio Approach to Understanding the Stereoselectivity of Reactions between Hydroxyalkyl Azides and Ketones

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A new stereoselective version of the Schmidt reaction has been discovered by Aubé and co-workers (*J. Am. Chem. Soc.* **2003**, *125*, 7914−7922). Quantum chemical calculations reported in this paper were carried out to examine the observed diastereoselectivities. The azide attack step is found to be reversible, but a thermodynamic preference for the equatorial attack product is observed. The final stereoselectivity of the reaction is determined by the axial/equatorial ratio of the chiral substituent in the resulting intermediate. In the case of 2-R-hydroxypropyl azides, interesting axial/equatorial preferences are observed. In particular, the phenyl substituent shows a preference for the axial position resulting from a novel interaction with a N_2 cationic group.

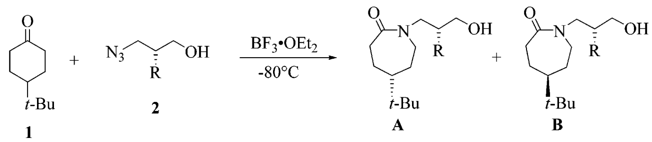
Introduction

Improvement of the selectivity and utility of an asymmetric reaction requires comprehension of the mechanism and the factors that influence asymmetry. Computational studies provide a useful means for achieving this end. Recently, a new diastereoselective reaction resulting in an *N*-hydroxyalkyl lactam was discovered (Scheme 1).[1−3] Amide moieties, particularly lactams, are common intermediates in natural product synthesis,[4] and this reaction provides a method for synthesizing them in a diastereoselectively pure form. We report here on a series of computations aimed at understanding the observed stereoselectivity.

Background

The reaction between hydroxyalkyl azides and ketones is a modification of the Schmidt reaction, which is commonly used to synthesize amides and lactams.[5−9] The classical Schmidt reaction is limited to the reaction of hydrazoic acid with a ketone or aldehyde (Scheme 2).

SCHEME 1



		A:B	yield
3	R = Me	74:26	98%
4	R = *i*Pr	88:12	85%
5	R = Ph	60:40	98%

Throughout the 1990s, it was shown that alkyl azides also react with both cations[10−15] and acid-activated carbonyl compounds[16−19] in Schmidt-like reactions that afford *N*-substituted amides or lactams. This work was further extended to include the reactions of hydroxyalkyl azides $HO(CH_2)_nN_3$ (where $n = 2$ or 3, with chain substitutions allowed) with ketones,[1,2,20,21] which as a class have a much broader scope than the corresponding reactions of simply alkyl azides.[22,23] Mechanistically, the hydroxyl group of the reagent first attacks the carbonyl

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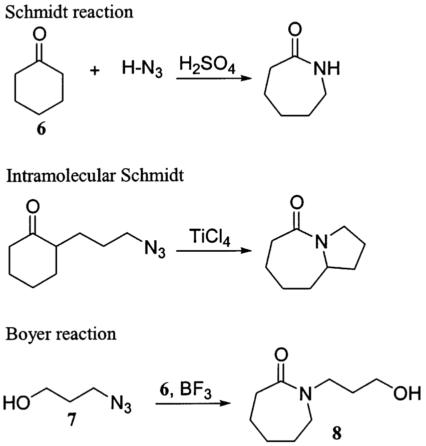
SCHEME 2



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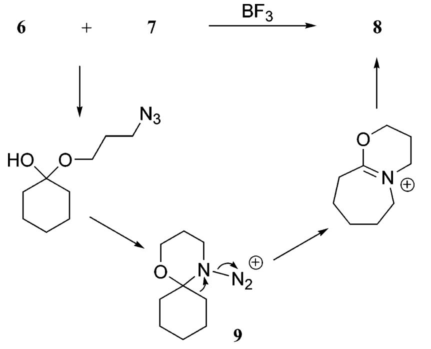

group to afford a hemiketal (Scheme 3). Subsequent dehydration forms an oxenium ion that undergoes intramolecular azide attack, forming an iminium ether intermediate. The reactions of hydroxyalkyl azides benefit from intramolecularity through the temporary "tethering" of the azide to the reactive carbonyl group and provide access to *N*-hydroxyalkyl lactams by simple hydrolysis or more highly substituted lactams when reacted with other nucleophiles.[24] In Scheme 3, the Criegee-type intermediate, **9**, contains two six-membered rings. In the following discussions, the original cyclohexane will be referred to as the carbocyclic ring. The heteratom-substituted six-membered ring will be referred to as the heterocyclic ring.

As mentioned above, this reaction can also proceed with diastereoselectivity. These can be as high as 96:4 (Schemes 1 and 4).[1] In these reactions, an achiral 4-substituted cyclohexanone is reacted with a chiral hydroxyalkyl azide. The reaction product is chiral, and the stereochemical course of the reaction depends on the hydroxyalkyl azide substituent. Both hydroxyethyl and hydroxypropyl azides have been used; however, this paper only focuses on the propyl azides. The substituent can be at either the 1, 2, or 3 position of the hydroxypropyl azide. Azides substituted on the 1 and 3 positions give much higher stereoselectivities than those observed for

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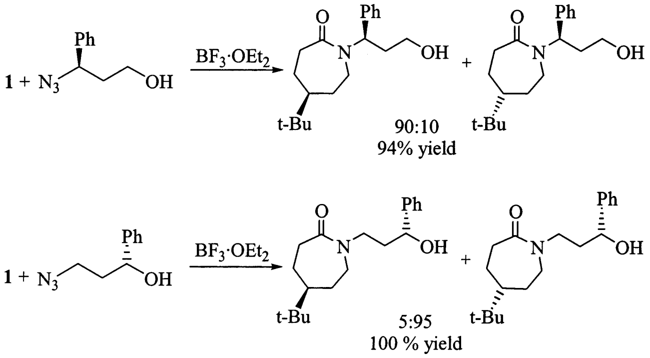

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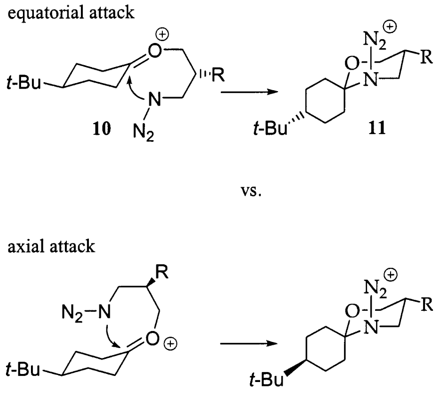

2-substituted reagents. In addition, the nature of the substituent at the 2 position can also affect selectivity. Surprisingly, methyl gives better results than phenyl (Scheme 1).

The proposed explanation for the diastereoselectivity of this reaction relies on a series of assumptions.[1−3] First, the azide must preferentially attack the carbonyl from the equatorial versus the axial position of a relatively fixed cyclohexyl ring; or, if the reaction is reversible, the product from equatorial attack must be lower in energy (Scheme 5). The second requirement is that migration must occur *anti*-periplanar (*app*) to the N_2 leaving group to allow maximum overlap between the σ-bonding orbital of the migrating group and the σ^*-orbital of the N_2 bond. When the N_2 group is equatorial, neither of the possible migratory groups can be *app* to it. Therefore, the N_2 group must occupy an axial position in the heterocyclic intermediate prior to migration (Scheme 6). These first two requirements do not depend on the location or identity of the substituent on the hydroxypropyl azide.

Third, the substituent R must have a preference for the axial or equatorial position in the transition state leading to product (Scheme 7). The transition-state energies are assumed to be reflected in those of their associated intermediates. The groups that are gauche and *app* to the N_2 leaving group switch positions when the heterocyclic ring flips. Thus, the methylene carbon that migrates in the equatorial conformer will be different from the one that migrates in the axial conformer. If there is no preference between the axial and equatorial positions in the intermediate, then no stereoselectivity will be observed. A strong equatorial preference by the R substituent will ensure that the majority of the

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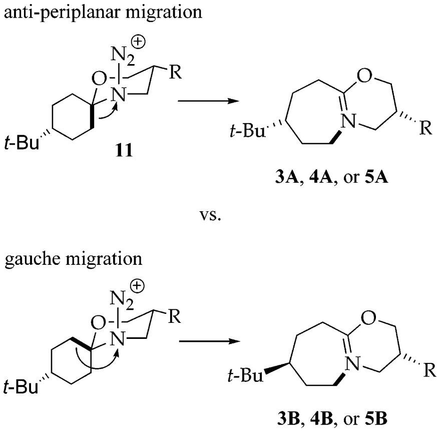
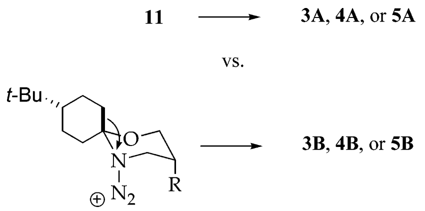
SCHEME 6



SCHEME 7



molecules are in an equatorial conformation, resulting in stereoselectivity.

The strong stereoselectivity observed for the 1- and 3-substituted hydroxypropyl azides is not surprising. Phenyl groups prefer the equatorial position by 2.9 kcal/mol in cyclohexane. At the reaction temperature of −82 °C, 99.9% of the intermediates should have the phenyl group equatorial. For the 2-substituted hydroxypropyl azides, the situation is less clear. The methyl substituent has a smaller preference for the equatorial position in cyclohexane (1.8 kcal/mol), resulting in lower selectivity during the reaction. Increasing the size of the substituent to isopropyl also increases the stereoselectivity, presumably because of the larger equatorial preference of this group. However, replacing the methyl with a phenyl substituent decreases stereoselectivity, and presumably the phenyl preference for the equatorial position is smaller. Normally, phenyl has a stronger preference for the equatorial position than methyl (2.9 kcal/mol versus 1.8 kcal/mol for cyclohexane). In such cases, Aubé and Katz have proposed a novel electrostatic interaction between the N_2^+ cation and the electron-dense phenyl ring that provides additional stabilization of the axial conformation, reducing the stereoselectivity.[25]

This paper investigates the validity of the above assumptions using quantum chemical calculations. In addition, the difference in stereoselectivity between 2-R = methyl and 2-R = phenyl will be investigated. The information provided by these calculations provides new insights into the stereoselectivity and will help improve the utility of this reaction.

Methodology

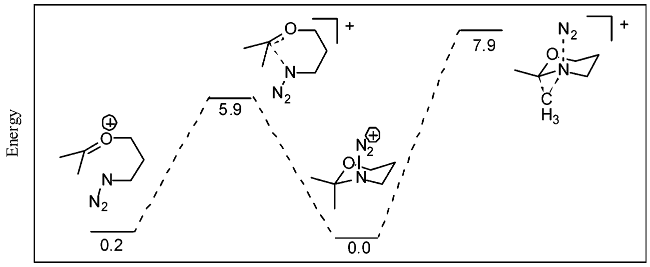
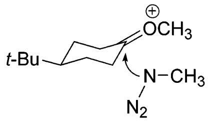


FIGURE 1. RHF/6-31G* potential energy surface for azide attack followed by methyl migration.

The Gaussian98[26] program was used to perform all calculations. The levels of theory and basis sets utilized were RHF/6-31G*, B3LYP/6-311G*, MP2/6-31G*, and MP2/6-311+G**//MP2/6-31G*. Frequency calculations were performed to confirm the identity of minima and transition states. In addition, the frequencies for both RHF/6-31G* and MP2/6-31G* were scaled based on the recommendations of Scott and Radom[27] and then used to convert the electronic energies to free energies.[28] The charges were calculated with the ChelpG algorithm[29] using the MP2/6-311+G**//MP2/6-31G* electron densities.

Results and Discussion

Azide Attack. The full system for azide attack, **10**, was too large for a single calculation and was divided into two smaller model systems, **12** and **13**. System **12**,



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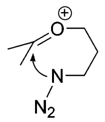

13

methyl azide attack on *O*-methyl-4-*tert*-butylcyclohexanone, does not include the tether and was used to calculate the energies for axial attack, equatorial attack, and the respective products. System **13** lacks the *tert*-butylcyclohexane, which is replaced by two methyl groups, and models the effect of the tether on azide attack. This compound was used to calculate the energy barriers for various steps in order to address the question of reversibility. The orientation of the attacking azide in **12** was chosen to match the calculations on the tethered system, **13**.

The RHF/6-31G*-calculated potential energy surface of **13** for both azide attack and subsequent methyl migration is shown in Figure 1. These results show that the azide attack step is most likely reversible. The

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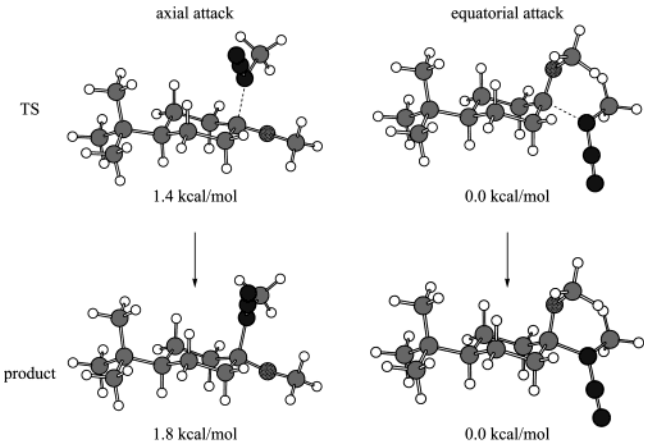

FIGURE 2. Comparison of the transition structures for axial attack and equatorial attack and the corresponding products (RHF/6-31G*).

migration barrier is 2.0 kcal/mol higher in energy than the barrier for ring opening (the reverse of azide attack). In this case, the thermodynamic stability of the equatorial product versus the axial product will determine the extent of stereoselectivity, rather than the height of the barrier for equatorial attack versus axial attack. However, it is still possible that circumstances other than energetics may prevent reversibility, so both the transition structures for azide attack and the resulting products were calculated.

The transition structure of **12** for equatorial attack is 1.4 kcal/mol lower in energy than axial attack at the RHF/6-31G* level of theory (Figure 2). This is not surprising, as a general preference for equatorial attack by large groups has been observed for many other reactions.[30] The product resulting from equatorial attack of **12** is 1.8 kcal/mol lower in energy than the axial product at the RHF/6-31G* level of theory (Figure 2). This results from steric interactions between the N_2 group and axial hydrogens in the axial attack product that are absent in the equatorial attack product. At a reaction temperature of −82 °C, the transition structure difference will result in 97.8% equatorial attack and 2.2% axial attack while the products predict 99.1% equatorial attack and 0.9% axial attack. So, regardless of whether the azide attack reaction is reversible, a strong preference for the equatorial product will be observed, allowing for the observed stereoselectivity.

***anti*-Periplanar Migration.** The same model system used for tethered azide attack, **13**, was also used to investigate migration tendencies. As seen in Figure 1, a transition structure was located 7.9 kcal/mol above the tetrahedral intermediate at the RHF/6-31G* level of theory. The $N-N_2$ bond is breaking, but the migration is in the very early stages. The vectors of the imaginary frequency are largest for the $N-N_2$ vibration and almost nonexistent for the migration motion. In contrast, the imaginary frequency vectors for the mechanistically similar Baeyer−Villiger reaction are significant for both bond-breaking and migration motions.[31] These results suggest that bond-breaking and migration may be stepwise in this modified Schmidt reaction. However, performing an IRC calculation on the Schmidt transition structure confirmed that bond-breaking and migration are concerted. In addition, we were unable to locate an intermediate for a stepwise process.

A lack of migration is observed in the transition structure because the migration is occurring between two positions on a cyclohexane ring and because the nitrogen is sp^3 hybridized in both the reactant and product. Normally, the migrating group can be *anti*-periplanar to the leaving group throughout the reaction; however, this is not possible for **13**. The migrating group initially occupies an axial position, but will occupy an equatorial position in the product. Therefore, the group must rotate away from its axial position during migration, reducing any interactions with the axial N_2 leaving group. In this situation, bond-breaking occurring before migration maximizes the stabilizing orbital interaction between the two groups. This accounts for the observed transition structure.

Attempts to locate a gauche transition structure were unsuccessful. Similar calculations for the Baeyer−Villiger reaction also indicated that gauche transition structures do not exist on the potential energy surface.[31] For the Baeyer−Villiger reaction, comparisons between *anti*-periplanar migration barriers and estimates of Baeyer−Villiger gauche migration barriers showed *app* migration to be favored by 5−25 kcal/mol at the B3LYP/6-311G* level of theory. Based on these results, the gauche migration is assumed to not be important for the reaction between hydroxyalkyl azides and ketones.

Conformations of the Heterocyclic Intermediate. Many theoretical calculations have been performed on cyclohexyl conformations. In particular, Wiberg et al. showed that RHF and B3LYP methods were unable to reproduce the experimental axial/equatorial preference of a phenyl ring.[32] In contrast, they found that the QCISD, and to a lesser extent the MP2 level of theory, gave results that compared more favorably to the experimental data.[33] However, due to our computational constraints, we decided to use MP2 rather than QCISD for our calculations. To choose a basis set, comparisons were made to the uncorrected QCISD calculated energy differences between equatorial and axial conformers, since Wiberg et al. used the same zero-point energy and thermal corrections for both their QCISD and MP2 calculations. MP2/6-311+G** was selected as the next optimal level of theory to use for cyclohexane conformer calculations (Table 1).[32,34] Comparison of the axial−equatorial energy difference for this level of theory and for QCISD gave 1.70 versus 1.76 for methylcyclohexane and 2.83 versus 2.95 for phenylcyclohexane. Model calculations showed negligible differences between MP2/6-311+G** and MP2/6-311+G**/MP2/6-31G* energies (data not shown). Thus, geometries were optimized at MP2/6-31G* and then the single point energies were

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TABLE 1. Relative Energy Difference (kcal/mol) between Axial and Equatorial Conformers for Methylcyclohexane and Phenylcyclohexane ($E_{ax} - E_{eq}$)[a]

level of theory	methyl[b]	phenyl
RHF/6-31G*	2.30	4.36[c]
B3LYP/6-31G*	2.13	3.69
MP2/6-31G*	1.90	2.88[c]
MP2/6-311G**	1.59	2.60
MP2/6-311+G**	1.70	2.83
QCISD/6-311+G(3df,2p)	1.76	2.95[c]
corrected QCISD	1.96	2.90[c]
experimental	1.80 ± 0.02	2.87 ± 0.3[d]

[a] Corrected QCISD has been adjusted for zero-point energy and temperature.[19,20] [b] Reference 34. [c] Reference 32. [d] Reference 33.

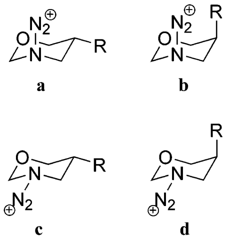
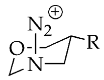


FIGURE 3. Four possible conformers of the tetrahedral intermediate model system **14**.

calculated with MP2/6-311+G**. The remainder of the calculations reported in this paper were performed with this level of theory.

Structure **14** was selected as an appropriate model system for intermediate **10**. Since the cyclohexyl reactant will occupy both equatorial and axial positions with respect to the heterocyclic intermediate, it was not included in the following calculations. There are four possible conformers for the heterocyclic intermediate model **14**: N_2^+ axial/R equatorial **14a**, N_2^+ axial/R axial **14b**, N_2^+ equatorial/R equatorial **14c**, and N_2^+ equatorial/R axial **14d** (Figure 3). Calculations were performed for R = methyl, isopropyl, and phenyl.



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The lowest energy conformation for the methyl and isopropyl substituents is Me or *i*-Pr equatorial and N_2^+ axial, **14a** (Table 2). However, we find this is reversed for the phenyl substituent and the axial position is preferred. Consequently, the lowest energy conformation is phenyl axial and N_2^+ axial, **14b**. Origins for this discrepancy are discussed below. The N_2^+ group prefers the axial position for R = methyl, isopropyl, and phenyl. This preference is most likely due to an electrostatic interaction between the N_2^+ group and the ring oxygen.[35] Similar axial preferences have been observed for other cationic substituents on tetrahydropyran.[35]

The relative free energy differences between the two lowest energy conformers were compared to the experimental data (Table 3). The experimental diastereomeric ratios were converted to a free energy difference using $\Delta G = -RT \ln K$ and $T = 191$ K (−82 °C), the temperature of the experiment. For R = methyl and R = isopropyl, the calculated conformational free energy differences (1.0 and 0.9 kcal/mol) are in good agreement with the experimental free energy differences (0.4 and 0.8 kcal/mol). Thus, the diastereomeric excess can be explained by the isopropyl group's and methyl group's preference for the equatorial position. These preferences are small enough that some of the ring-flip conformer is present at the temperature of the experiment, resulting in the low diastereoselectivity.

TABLE 2. Relative Energies (kcal/mol) of the Conformers of the Heterocyclic Intermediate Model 14 (see Figure 2)

R = methyl	**a**	**b**	**c**	**d**
RHF/6-31G*	0.0	1.8	3.0	4.0
MP2/6-31G*	0.0	0.9	3.3	3.7
MP2/6-311+G**//MP2/6-31G*	0.0	0.8	3.1	3.6

R = isopropyl	**a**	**b**	**c**	**d**
RHF/6-31G*	0.0	2.5	3.1	4.6
MP2/6-31G*	0.0	0.7	3.4	3.8
MP2/6-311+G**//MP2/6-31G*	0.0	0.6	3.2	3.7

R = phenyl	**a**	**b**	**c**	**d**
RHF/6-31G*	0.0	0.3	3.0	N/A
MP2/6-31G*	2.2	0.0	5.6	6.6
MP2/6-311+G**//MP2/6-31G*	2.2	0.0	5.8	6.5

TABLE 3. Comparison of the Relative Free Energy Difference (kcal/mol) between Axial and Equatorial Conformers of 14 ($E_{ax} - E_{eq}$) to the Experimentally Observed Diastereomeric Ratios

level of theory	methyl	isopropyl	phenyl
RHF/6-31G*	1.9	2.6	0.7
MP2/6-31G*	1.1	1.0	−1.8
MP2/6-311+G**//MP2/6-31G*	1.0	0.9	−1.7
experimental ratio	74:26	88:12	60:40
experimental ΔG	0.4	0.8	0.1

The calculations show no difference between the isopropyl substituent and the methyl substituent energy differences. This is also observed for C-5-substituted 1,3 dioxanes experimentally (Me = 0.80 and *i*-Pr = 0.98).[35] In contrast, the experimental numbers for the azide reaction indicate that the isopropyl substituent has a slightly larger energy difference than methyl. The level of theory being employed is not accurate enough to reproduce such a slight difference but is able to reproduce the approximate magnitude of the energy differences for both substituents.

For R = phenyl, the calculated relative free energy difference between the two lowest energy conformers does not match the experimental data. In fact, the calculations predict a preference opposite of what is observed. This difference may be a result of comparing gas-phase calculations to solution experimental data. Even though the solvent is nonpolar (CH_2Cl_2), it can still shield electrostatic interactions reducing their strength. It is believed that the phenyl axial preference is mainly a result of electrostatics (see below). Thus, inclusion of solvent could reduce the energy difference between axial and equatorial conformers. In contrast, solvent is not expected to affect the methyl or isopropyl energy differences since they are determined mainly by steric interactions. So far, attempts to include solvent, using standard

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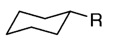
solvent models in Gaussian98, such as PCM,[36,37] IPCM,[38] and SCIPCM,[38] have been unsuccessful due to convergence problems.

Six-Membered-Ring Conformer Stabilities. The unusual preference of the phenyl group for the axial position and the preference of the N_2^+ group for the axial position for both R = methyl and R = phenyl was investigated further. Several model systems were designed to calculate the importance of the different interactions that could contribute to the observed conformational energies. The specific comparisons studied were (1) R-cyclohexane **(15)** versus 3-R-tetrahydropyran (**16**), (2) *N*-diazoniumpiperidine (**17**) versus *N*-diazonium-1,3-tetrahydrooxazine (**18**), and (3) R-cyclohexane (**15**) versus 3-R-*N*-diazoniumpiperidine (**19**) where R = methyl or phenyl.



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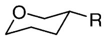

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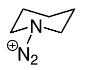

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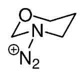

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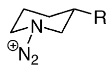

19

The effect of replacing a carbon with oxygen at the 3-position of a cyclohexane ring on the axial/equatorial energy difference has been studied.[30] The axial conformer of 3-substituted tetrahydropyran lacks an axial hydrogen, decreasing the steric hindrance of this conformer and the energy difference between the equatorial and axial conformations. This effect has been well documented for 3-methyltetrahydropyran (**16**, R = methyl), both experimentally[39-41] and theoretically.[42,43] For methylcyclohexane, **15**, the experimental axial/equatorial energy difference is 1.80 kcal/mol at 298 K. Experimental values for this difference in **16** range from 1.27 at 170 K to 1.49 kcal/mol at 303 K. Comparison of the energy differences for **15** and **16** show that addition of the oxygen atom to the ring causes a decrease of 0.31 to 0.53 kcal/mol in the equatorial preference. Theoretical calculations of **16** give values from 1.36 to 1.76 kcal/mol at 298 K for the axial/equatorial energy difference, depending on the level of theory. Our MP2/6-311+G**//MP2/6-31G* calculations give a ΔG of 1.3 kcal/mol, which is in good agreement with experiment (Table 4).

For phenyl, our calculations indicate that the inclusion of oxygen causes the ΔE to drop from 2.8 kcal/mol to 0.9 kcal/mol and the ΔG to drop from 3.4 kcal/mol to 1.4 kcal/mol. In fact, the axial/equatorial relative energy difference is the same for methyl- and phenyl-substituted tetrahydropyran. For the phenyl substituent, not only is steric hindrance reduced by removal of an axial hydrogen, but also the phenyl ring rotates with respect to the cyclohexane ring further reducing steric interactions with the remaining axial hydrogen (Figure 4). This new orientation reduces the energy of the axial conformer further by providing an electrostatic interaction between the oxygen and a phenyl hydrogen. Several recent theoretical and experimental papers support the presence of C—H- - -O hydrogen bonds.[44-47] The distance between the O and H is 2.28 Å, well with in the distance for a hydrogen bond. In addition, the change in the ChelpG charge of the oxygen atom on going from equatorial to axial is −0.023, which is in accordance with the presence of a hydrogen bond in the axial conformer.[48]

TABLE 4. Relative Energy Differences (kcal/mol) between Axial and Equatorial Conformers ($E_{ax} - E_{eq}$) for R-Cyclohexane (15) and R-Tetrahydropyran (16) (R = Methyl or Phenyl)[a]

	cyclohexane		tetrahydropyran	
level of theory	methyl	phenyl	methyl	phenyl
RHF/6-31G*	2.3	4.4	1.4[b]	4.0
MP2/6-31G*	1.9	2.9	0.9[c]	−0.3
MP2/6-311+G**//MP2/6-31G*	1.7 (1.9)	2.8 (3.4)	1.1 (1.3)	0.9 (1.4)
experimental	1.8	2.9	1.3−1.5[d]	N/A

[a] The numbers in parentheses are relative free energy differences (kcal/mol). [b] Reference 42. [c] Reference 43. [d] References 39−41.

FIGURE 4. Overlap of the MP2/6-31G* structures of phenylcyclohexane (gray) and 3-phenyloxirane (black). The arrow indicates the position that has been substituted with oxygen.

Next, the effect of oxygen substitution on the conformational preference of the N_2^+ substituent was investigated. Surprisingly, the N_2^+ group has no preference for the equatorial or axial position for unsubstituted cyclohexane **17** (Table 5). Presumably, the replacement of an axial hydrogen with the linear N_2^+ group does not cause an increase in steric hindrance. This is comparable to what is observed for CN ($\Delta G = 0.15-0.25$), another linear substituent.[30] Substitution of the oxygen should therefore have no effect on the N_2^+ preference, since 1,3-diaxial interactions are unimportant in this situation. In fact, an effect is observed and the axial conformer is preferred by 3.1 kcal/mol for **18**. As mentioned earlier,[35] the axial

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TABLE 5. Relative Energy Differences (kcal/mol) between Axial and Equatorial Conformers ($E_{ax} - E_{aq}$) for *N*-Diazoniumpiperidine (17) and *N*-Diazonium-1,3-tetrahydrooxazine (18)

level of theory	**17**	**18**
RHF/6-31G*	1.1	−2.8
MP2/6-31G*	0.1	−3.1
MP2/6-311+G**//MP2/6-31G*	0.2	−3.1

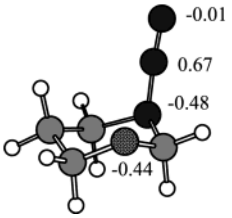

FIGURE 5. ChelpG charges from MP2/6-311+G**//MP2/6-31G* for **18**.

TABLE 6. Relative Energies (kcal/mol) of the Conformers of 3-R-*N*-Diazoniumpiperidine (19) (See Figure 3)

R = methyl	**a**	**b**	**c**	**d**
RHF/6-31G*	1.0	2.9	0.0	1.7
MP2/6-31G*	0.0	1.3	0.0	1.2
MP2/6-311+G**//MP2/6-31G*	0.0	1.2	0.1	1.0
R = phenyl	**a**	**b**	**c**	**d**
RHF/6-31G*	1.0	2.8	0.0	4.4
MP2/6-31G*	1.0	0.0	1.6	3.7
MP2/6-311+G**//MP2/6-31G*	2.0	0.0	2.1	4.1

conformational preference can be explained by electrostatics. A strong interaction is possible between the negatively charged oxygen and the positive N_2^+ group in the axial conformer. Examination of the partial charges confirms this assumption (Figure 5). This interaction is greatly reduced in the equatorial conformer by distance (O−N: 2.90 versus 3.45 Å, respectively).

Finally, the effect of adding an N_2^+ group and nitrogen to the ring was investigated for phenyl and methyl conformers. 3-R-*N*-diazoniumpiperidine **19** has the same possible conformers as the heterocyclic intermediate model **14**. The computational results are presented in Table 6. As expected, the two lowest energy conformers for R = methyl have the methyl equatorial and the N_2^+ group axial or equatorial. As seen earlier, the N_2^+ group shows no preference between the equatorial and axial positions, even when the methyl is axial.

The situation for R = phenyl is very different with a clear preference for the **19b** conformation being observed. This conformer is at least 2.0 kcal/mol lower in energy than the other conformers. For the equatorial phenyl conformers, **19a** and **19c**, the N_2^+ group again does not demonstrate a preference for axial or equatorial, as is the case for R = methyl. If the pattern followed by R = methyl was continued for R = phenyl, one would expect conformer **19b** to have the same energy as the **19d** conformer. Instead, **19b** is 4.1 kcal/mol lower in energy than the **19d** conformer. In the **19b** structure, the phenyl ring is aligned to interact with the N_2^+ cation, stabilizing this conformer. The stabilization of a cation by a phenyl ring is a known effect.[49,50] Again, examination of the ChelpG partial charges supports this conclusion (Figure 6).

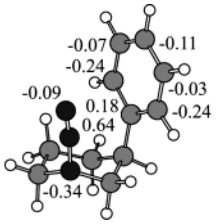

FIGURE 6. ChelpG charges from MP2/6-311+G**/MP2/6-31G* for **19**, R = phenyl.

Combining the results from the above comparisons indicates which interactions are the most important in determining the R substituent axial/equatorial energy difference of the intermediate model **14** when compared to cyclohexane. In the case of R = methyl, comparison to cyclohexane shows that the presence of the ring nitrogen and the N_2^+ group have little to no effect on the axial/equatorial difference. Thus, the interaction between the methyl and N_2^+ group is an unimportant one. This is not true of the ring oxygen and methyl interaction. Oxygen substitution causes a slight decrease in the energy difference. This substitution also switches the N_2^+ group preference to axial.

In the case of R = phenyl, much larger effects are observed. The interaction between the N_2^+ group and the phenyl group is large enough to cause the preference of phenyl to switch from equatorial in cyclohexane to axial in **19**. One would assume that including the oxygen substitution would increase the axial preference even further, based on comparisons between cyclohexane and **16**. However, this is not observed; the energy difference between axial and equatorial does not change between **19** and **14**. The beneficial reduction in sterics caused by the phenyl ring rotation observed for the minimum structure of **16** is less likely in the minimum structure of **14**, since this disrupts the stabilizing cation-π interaction. Therefore, oxygen substitution has no effect on the phenyl group axial/equatorial preference. The oxygen does have the expected effect on the N_2^+ group, in that the relative energies of the N_2^+ equatorial conformers, **19c** and **19d**, increase with respect to the N_2^+ axial conformers, **19a** and **19b**.

Conclusion

A greater understanding of the stereoselectivity in the reaction between hydroxyalkyl azides and ketones has been achieved. Our calculations have confirmed the three initial hypotheses for explaining the observed diastereoselectivity: (1) The equatorial azide attack intermediate is preferred over the axial both kinetically and thermodynamically. (2) The migratory group is *app* to the N_2 leaving group, and migration and N−N_2 bond-breaking are concerted. (3) The diastereoselectivity is determined by the extent of the equatorial preference of the R substituent. For the 2-R-hydroxypropyl azides, this preference is a result of several different interactions. For R

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= methyl, the oxygen substitution in the ring has the largest effect while for R = phenyl, the addition of the N_2^+ group is most important. The latter is particularly noteworthy as it involves a novel electrostatic interaction between the phenyl substituent and the N_2^+ group.

Further studies of this system will involve the addition of solvent to the calculations. As mentioned above, we predict that the inclusion of solvent will have little effect on the axial/equatorial energy difference for R = methyl and R = isopropyl, since these are determined solely by steric interactions or the lack thereof. However, large differences between solvent and gas-phase results should be observed for R = phenyl, since electrostatic interactions play an important role in the axial/equatorial energy difference.

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Supporting Information Available: Tables of Cartesian coordinates and energies for **12TS**, **12P**, **13R**, **13TS1**, **13I**, **13TS2**, **14a**, **16**−**18**, and **19a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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