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The effect of solvent on the stereoselectivity of reactions between hydroxyalkyl azides and ketones

Anna K. Manukyan, Jennifer L. Radkiewicz-Poutsma *

Department of Chemistry and Biochemistry, Old Dominion University, 4541 Hampton Boulevard, Norfolk, VA 23529, USA

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Abstract

Reactions between achiral 4-substituted cyclohexanones and chiral hydroxyalkyl azides can give asymmetric ring expansion products. Previously, we carried out quantum chemical calculations on the reactions involving 2-R-hydroxypropyl azides to determine the cause of the observed diastereoselectivities. We found that the axial/equatorial ratio of the chiral substituent in the resulting heterocyclohexyl intermediate was the controlling factor. However, our predicted product ratio for 2-phenylhydroxypropyl azide did not agree well with experiment. We attributed this problem to the lack of solvent in our calculations, since the phenyl axial/equatorial ratio was strongly influenced by a cation-π interaction, which should be shielded in solvent. Therefore, we have added solvent via the CPCM method to our previous calculations. We observed little change in the predicted selectivities for R = Me or *i*-Pr, which are close to their experimental values. For R = Ph, we now predict essentially no preference for either diastereomer, in agreement with experiment. Surprisingly, the charge–dipole interaction between the oxygen and N_2^+ group was less affected by solvent than the cation-π interaction. In addition, a possible gas-phase electrostatic interaction between the methyl group (R = Me) and the cationic N_2 group was revealed.

Keywords: Diastereoselectivity; Schmidt reaction; Cation-π interactions; CPCM

1. Introduction

Recently, Aubé and co-workers discovered a stereoselective pseudo-intramolecular Schmidt reaction (Fig. 1) [1]. The Schmidt reaction is commonly used to synthesize a variety of nitrogen containing compounds, particularly lactams [2]. Thus, this stereoselective version could prove to be a very useful synthetic tool. The mechanism involves initial attack at the activated ketone by the hydroxyl group to produce a hemiketal (Fig. 1). An intramolecular reaction between the azide and the oxonium ion then occurs. Hydrolysis of the resulting iminium ion provides the *N*-hydroxyalkyl amide.

In order to better understand the stereoselectivities of this reaction, we performed a series of ab initio calculations on model systems [3]. In particular, we wished to determine if the diastereoselectivities were affected by a cation-π interaction. The R substituent (R = Me, *i*-Pr, or Ph) can occupy either an axial or equatorial position in the heteroatom-substituted cyclohexane ring of the intermediate (Fig. 1). A lack of preference between the two positions will lead to low stereoselectivity. Thus, replacing methyl with a bulkier isopropyl shows a slight increase in stereoselectivity from 74:26 to 88:12. However, the switch to an even bulkier phenyl group causes a decrease to 60:40. A stabilizing cation-π interaction between the positively charged N_2 group and the phenyl ring, which is strongest when both groups are axial, could explain this discrepancy [1c,4].

Our calculations, which used compound **6** as a model of intermediate **5** (Fig. 2), confirmed that the cation-π interaction was important in determining the diastereoselective ratio for the 2-phenyl substitutent [3]. As a reminder, the phenyl group prefers the equatorial position by 2.9 kcal/mol in cyclohexane [5]. In contrast, we found the conformer of **6** with both the N_2^+ group and the phenyl ring in axial positions to be the lowest in energy by 2.0 kcal/mol (Table 1). The cation-π interaction causes a switch in the phenyl group preference from equatorial to axial.

We evaluated the accuracy of our results by comparing the free energy difference between the axial and equatorial conformers ($\Delta G_{\text{ax-eq}}$) with ΔG_{expt}, which was determined from the experimental selectivities [1c], using the equation $\Delta G = -\text{RT} \ln K$ (Table 1). One failure of our calculations was

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* Corresponding author. Tel.: +1 757 683 4101.
E-mail address: jradkiew@odu.edu (J.L. Radkiewicz-Poutsma).

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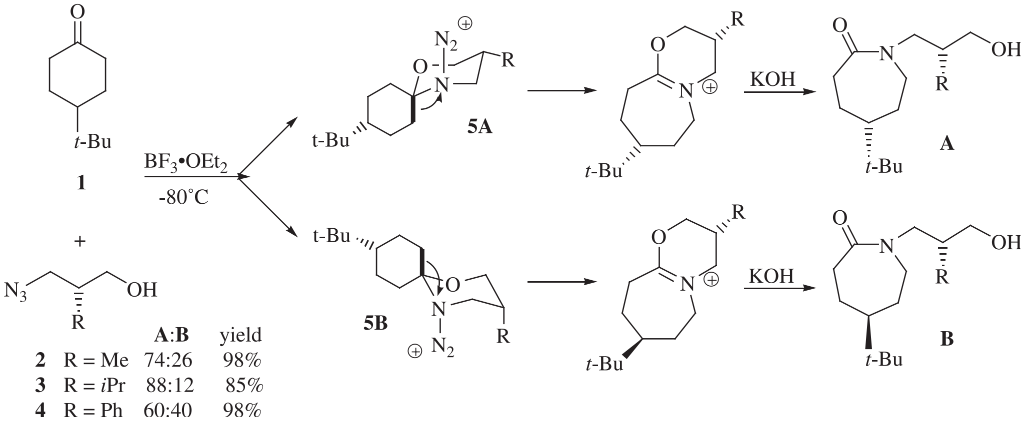

Fig. 1. The mechanism and diastereoselectivities for the reaction between 4-*t*-butylcyclohexanone and 2-R-hydroxypropyl azide.

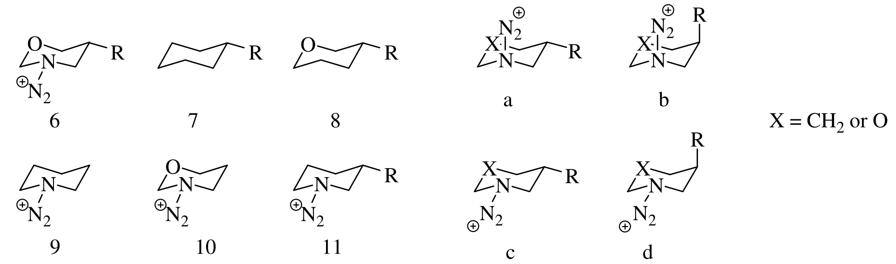

Fig. 2. The chemical structures of the intermediate model (**6**), R-cyclohexane (**7**), 3-R-tetrahydropyran (**8**), *N*-diazoniumpiperidine (**9**), *N*-diazonium-1, 3-tetrahydrooxazine (**10**), and 3-R-*N*-diazoniumpiperidine (**11**) and the four possible conformers for **6** and **11**.

the significant difference of 2.1 kcal/mol between our calculated free energy for phenyl and the experimental value [3]. We predict the axial conformer to be preferred, while the experimental results indicate that there should be essentially no preference. All other computed $\Delta G_{\text{ax-eq}}$ values were within 0.7 kcal/mol of the corresponding experimental values (Table 1), indicating that the MP2/6-311+G(d,p)// MP2/6-31G(d) level of theory is extremely accurate (< 1 kcal/mol) for these types of calculations. However, this level of theory was not good enough to reproduce the stereoselectivity trend for R=Me and R=*i*-Pr observed in the modified Schmidt reaction, nor did we expect it to.

We attributed the bad performance of our method for **6** with R=Ph to the lack of solvent in these calculations. These reactions were performed in CH_2Cl_2 [1], which has a dielectric constant of 8.93. Thus, the solvent should still provide some shielding of electrostatic interactions despite being non-polar. The $\Delta G_{\text{ax-eq}}$'s for R=Me or *i*-Pr, which are dependent on sterics should only be slightly affected by the inclusion of solvent, whereas the $\Delta G_{\text{ax-eq}}$ for R=Ph should be significantly affected when solvent is added. Calculations by other groups on cation-π interactions have shown that going from the gas-phase to a low dielectric solvent can have a significant effect on the interaction energy [9].

Previously, our attempts to include the various solvent models in GAUSSIAN 98 [10] had been unsuccessful due to convergence problems. However, we were eventually able to perform these calculations with the conductor-like polarizable continuum method (CPCM) [11]. We have also been able to perform solvent calculations using the modified versions of CPCM in GAUSSIAN 03 [12]. We report here on the inclusion of solvent models in our previous gas-phase calculations and the improved agreement between our results and the experimental

Table 1
Comparison of MP2/6-311+G(d,p)//MP2/6-31G(d) $\Delta G_{ax-eq's}$ with the experimental values

Compound	ΔG_{gas}	ΔG_{exp}	$\Delta G_{\text{gas}} - \Delta G_{\text{exp}}$
Methylcyclohexane	1.9	1.8[a]	0.1
Phenylcyclohexane	3.4	2.9[b]	0.5
3-Methyltetrahydropyran	1.3	1.3–1.5[c]	0.0–0.2
5-Methyl-1,3-dioxane	0.8	0.8[d]	0.0
5-Isopropyl-1,3-dioxane	0.9	1.0[d]	0.1
Intermediate **6**, R=Me	1.1[e]	0.4[f]	0.7
Intermediate **6**, R=*i*-Pr	0.9	0.8[f]	0.1
Intermediate **6**, R=Ph	−2.0[e]	0.1[f]	2.1

The ΔG_{exp} listed for intermediate **6** was taken from the diastereoselectivities and not from axial/equatorial energy differences.

[a] Ref. [6].

[b] Ref. [5].

[c] Ref. [7].

[d] Ref. [8].

[e] These numbers are slightly different from those reported in Ref. [3], as it was discovered that RHF/6-31G* geometries had been used for the MP2/6-311+G** single point calculations for **6b** R=Me and **6a** R=Ph, instead of the MP2/6-31G* geometries.

[f] Ref. [1c].