

# Experimental and Theoretical Study of Reduction Reaction of *Cis* and *Trans* 4-*tert*-butyl-2-*X*-ciclohexanone (*X* = F and Cl) With *N*-selectride

## *Estudo Experimental e Teórico da Reação de Redução do Cis e Trans 4-tert-butil-2-X-Ciclohexanona (X = F e Cl) com N-selectride*

Pedro R. Anizelli<sup>a,\*</sup> 

<sup>a</sup>Instituto Federal do Paraná, CEP 86400-000, Jacarezinho-PR, Brazil.

\*E-mail: [pedro.anizelli@ifpr.edu.br](mailto:pedro.anizelli@ifpr.edu.br)

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The study of diastereoselective in reduction reaction of 4-*tert*-butyl-2-*X*-ciclohexanone (*X*=F and Cl) with *N*-Selectride were obtained by means of experimental results and theoretical calculations. For substituents in *axial* position in carbon 2 was obtained the *equatorial* alcohol and theoretical calculations of transition state showed that approximation of reducing reagent by *axial* face is favorable than approximation by *equatorial* face. However, for substituents in *equatorial* position was obtained the *axial* alcohol because the approximation of reducing by *equatorial* face is favorable than approximation by *axial* face. The electronic effects like Cieplak model and higher ring torsion angle were used to explain the experimental results observed.

**Keywords:** Diastereoselective; ketone; Theoretical Calculations;

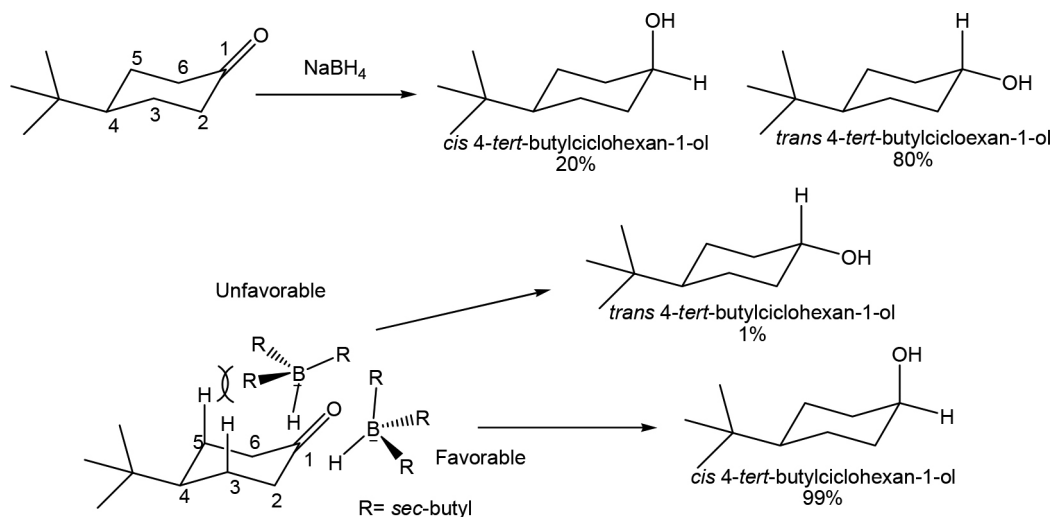
## 1. Introduction

The diastereoselective study in reduction reaction of carbonyl compounds is a important topic in synthesis of molecules with biological activity,<sup>1</sup> because is desirable the achievement of products with high amounts of one the stereoisomers. Recently<sup>2-4</sup>, some works related the importance of theoretical calculation using density functional theory (DFT) to understand the selective reduction of prochiral ketone.

The use of lithium aluminum hydride LiAlH<sub>4</sub> reactant for the reduction of ketones and aldehydes is standard protocol in synthetic organic chemistry. Observation of stereoselectivity in the reduction of prochiral ketones is well known, and several models have been proposed to explain the results<sup>5</sup>. Another widely used reactant in reduction reaction is sodium borohydride (NaBH<sub>4</sub>), but one limitation of this reactant is the low stereoselectivity for some substrates.<sup>6-8</sup> However, some papers<sup>9,10</sup> shows that some reduction reaction with these reducing reactants may occur with high stereoselectivity, where cations like Li<sup>+</sup>, Na<sup>+</sup> or transitions metals<sup>11</sup> participate in transition state inducing the selectivity in the reduction.

A class of compounds that are selective in reduction of ketones are the metals of tri-*sec*-butylborohydride (selectrides), because the bulk group (tri-*sec*-butyl), present in this reactant allows that the attack is preferential in one of face of carbonyl group, due the steric effects.<sup>1</sup> This reactant has been used in synthesis of compounds of biological interest, because of stereoselectivity in reduction that is one the steps in the synthetic route.<sup>12-15</sup> Studies showed that, some reduction reaction with these reducing reactants, like *N*-selectride and *L*-selectride, the counterion Na<sup>+</sup> and Li<sup>+</sup> showed an important effect in diastereoselective reaction, due the chelation in transition state, inducing the preferential formation of one of the stereoisomers. The Selectride reagents exhibit the expected trends: if chelating carbonyl compounds accelerate the rate of reduction, then the reaction is highly stereoselective.<sup>16,17</sup>

The theories, that consider electronic effects, used to explain diastereoselectivity in reduction reaction are the Felkin-Ahn<sup>18</sup> and Cieplak model.<sup>19</sup> The former found that the bond vicinal to the reaction center, which contained strongest electron withdrawing group, C<sub>2</sub>-X, should lie antiperiplanar to the incipient bond in order to maximize the  $\sigma_{C...Nu} \rightarrow \sigma_{C-X}^*$  orbital interaction in transition state. The Cieplak model states that the strongest electron donation group should lie antiperiplanar to the incipient bond in order to maximize the  $\sigma_{C-X} \rightarrow \sigma_{C...Nu}^*$  orbital interaction in transition state. Other actors<sup>20,21</sup> proposed that the  $\pi$ -facial diastereoselection in nucleophilic addition is based on the simple assumption that LUMO carbonyl lobe is larger on *axial* than *equatorial* face.



**Figure 1.** Reduction of 4-*tert*-butylcyclohexanone with NaBH<sub>4</sub> and selectrides

Reduction reaction was object of study using ketone with high bias conformational like the 4-*tert*-butylcyclohexanone (Figure 1).<sup>22</sup> The not bulky reactants like sodium borohydride, provide diastereoselective yielding *equatorial* alcohol in higher amounts. Bulky reactants like tri-*sec*-butylborohydride provides the *axial* alcohol in higher amounts (Figure 1), due the steric hindrance between *axial* hydrogen 3 and 5 and the bulk group *sec*-butyl that occur in approximation by *axial* face.<sup>23</sup> However, with the same reducing, other work<sup>24</sup> observed the predominate formation of *equatorial* alcohol in the ketone with *i*-Propyl in *axial* position in carbon 2. This result was attributed to higher steric hindrance in approximation by *equatorial* face than *axial* face.

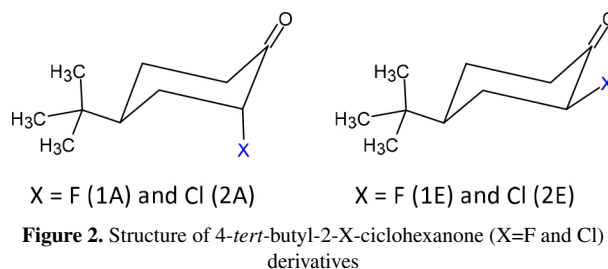
A study in the reduction of 4-*tert*-butyl-2-X-cyclohexanone<sup>25</sup> with LiAlH<sub>4</sub> showed with equatorial substituents yields increasing amounts of axial alcohol in the series for X (H<CH<sub>3</sub><Br<Cl<F<<OCH<sub>3</sub>), while with *axial* substituents yields increasing amounts of axial alcohol in the series (Cl<Br<CH<sub>3</sub><OCH<sub>3</sub><H<F). The Felkin-Ahn theory<sup>18</sup> and repulsion between the nucleophile and the X group were invoked for explain this results. Electrostatic interaction, also was used for explaining the diastereoselectivity in electrophilic addition.<sup>26</sup>

The present work aims to study by theoretical and experimental results the reduction reaction of *trans* and *cis* of 4-*tert*-butyl-2-X-cyclohexanone (X = F and Cl) (Figure 2) with N-selectride. To rationalize the experimental data was make theoretical calculations of transition state and NBO analyses.

## 2. Experimental

### 2.1. Computational details

All structures of products and transition state were optimized using hybrid functional B3LYP<sup>27-29</sup> and basis set aug-cc-pVDZ<sup>30</sup> with program package Gaussian03.<sup>31</sup>



**Figure 2.** Structure of 4-*tert*-butyl-2-X-cyclohexanone (X=F and Cl) derivatives

The basis set aug-cc-pVDZ was chosen for the correct description of fluorine, chlorine, bromine and oxygen. This basis set includes additional diffuse functions (aug prefix), which were used to take into account the nature of lone pairs. The transition state was characterized by negative imaginary frequency that correspond to hydride vibration from atom B toward to carbonyl carbon. Electronic structures from transition states were studied using NBO analysis<sup>32</sup> at the B3LYP/cc-pVDZ level using the geometries optimized.

### 2.2. Synthesis

- Synthesis of 4-*tert*-butyl-2-fluorocyclohexanone:<sup>33</sup> The reaction between 4-*tert*-butylcyclohexanone (0.9 g, 6.0 mmol) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2,2,6]octane bis(tetrafluoroborate) (2.3 g, 6.6 mmol) in acetonitrile yielding the 1A and 1E isomers, which were separated by column chromatography (hexane/acetate 8:2).
- Synthesis of 4-*tert*-butyl-2-chlorocyclohexanone:<sup>34, 35</sup> The reaction between 4-*tert*-butyl-cyclohexanone (1.0 g, 6.4 mmol) and gaseous Cl<sub>2</sub> (0.8 g, 11.2 mmol) in dry tetrahydrofuran yielding the 2A and 2E isomers, which were separated by column chromatography (hexane/acetate 8:2).
- Reduction of the 1A and 2A isomers of 4-*tert*-butyl-2-X-cyclohexanone (X = F and Cl):<sup>36,37</sup> The reaction (Figure 3) was carried out between the ketone and reducing reactant N-selectride yielding the product *cis*-4-*tert*-

butyl-2-X-cyclohexan-1-ol with 21% of yield for the fluorine derivative and 81.5 % for the chlorine derivative. The product with relative stereochemistry *trans*, to carbons 1 and 2, for 4-*tert*-butyl-2-X-cyclohexan-1-ol was not observed in detectable amounts in the reduction with N-selectride.

**3A:**  $^1\text{H NMR}$  ( $\text{CD}_2\text{Cl}_2$ , 400 MHz)  $\delta$  in ppm (NMR spectra available in supporting information): 0,86 (9H,  $\text{H}_8$ , s), 1,01 (1H,  $\text{H}_{5\text{ax}}$ , m), 1,29 (1H,  $\text{H}_{3\text{ax}}$ , m), 1,42 (1H,  $\text{H}_{4\text{ax}}$ , m), 1,59 (1H,  $\text{H}_{6\text{ax}}$ , m), 1,82 (1H,  $\text{H}_{5\text{eq}}$ , m), 1,85 (1H,  $\text{H}_{6\text{eq}}$ , m), 2,17 (1H,  $\text{H}_{3\text{eq}}$ , m), 3,46 (1H,  $\text{H}_{1\text{ax}}$ , dddd;  $J = 2,2$  Hz; 4,7 Hz; 11,8 Hz; 28,9 Hz), 4,80 (1H,  $\text{H}_{2\text{eq}}$ , m).

$^{13}\text{C RMN}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  in ppm (NMR spectra available in supporting information): 24,9 ( $\text{C}_5$ ), 27,1 ( $\text{C}_8$ ), 29,6 ( $\text{C}_6$ ), 31,0 ( $\text{C}_3$ ), 31,6 ( $\text{C}_7$ ), 40,3 ( $\text{C}_4$ ), 71,1 ( $\text{C}_1$ ), 92,5 ( $\text{C}_2$ ).

**4A:**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  in ppm (NMR spectra available in supporting information): 0,86 (9H,  $\text{H}_8$ , s), 1,06 (1H,  $\text{H}_{5\text{ax}}$ , m), 1,53 (1H,  $\text{H}_{4\text{ax}}$ , m), 1,57 (1H,  $\text{H}_{6\text{ax}}$ , m), 1,66 (1H,  $\text{H}_{5\text{eq}}$ , m), 1,80 (3H), 2,18 (1H,  $\text{H}_{3\text{eq}}$ , m), 3,64 (1H,  $\text{H}_{1\text{ax}}$ , ddd  $J = 3,9$  Hz; 7,6 Hz; 11,3 Hz), 4,57 (1H,  $\text{H}_{2\text{eq}}$ , m).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  in ppm (NMR spectra available in supporting information): 25,2 ( $\text{C}_5$ ), 27,5 ( $\text{C}_8$ ), 29,7 ( $\text{C}_6$ ), 31,8 ( $\text{C}_3$ ), 33,9 ( $\text{C}_7$ ), 39,8 ( $\text{C}_4$ ), 67,1 ( $\text{C}_1$ ), 71,3 ( $\text{C}_2$ ).

d) Reduction of 1E and 2E isomers of 4-*tert*-butyl-2-X-cyclohexanone (X = F and Cl):<sup>36,37</sup> The reaction (Figure 4) was carried out between the ketone and reducing reactant N-selectride yielding the product *cis*-4-*tert*-butyl-2-X-cyclohexan-1-ol with 56.2% of yield for the fluorine derivative and 74.5 % for the chlorine

derivative. The product with relative stereochemistry *trans*, to carbons 1 and 2, for 4-*tert*-butyl-2-X-cyclohexan-1-ol was not observed in detectable amounts in the reduction with N-selectride.

**3E:**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  in ppm (NMR spectra available in supporting information): 0,90 (9H,  $\text{H}_8$ , s), 1,08 (1H,  $\text{H}_{4\text{ax}}$ , m), 1,27 (1H,  $\text{H}_{6\text{ax}}$ , m), 1,36 (1H,  $\text{H}_{5\text{ax}}$ , m), 1,46 (1H,  $\text{H}_{5\text{eq}}$ , m), 1,65 (1H,  $\text{H}_{3\text{ax}}$ , m), 1,88 (1H,  $\text{H}_{3\text{eq}}$ , m), 2,02 (1H,  $\text{H}_{6\text{eq}}$ , m), 4,16 (1H,  $\text{H}_{1\text{eq}}$ , m), 4,51 (1H,  $\text{H}_{2\text{ax}}$ , dddd  $J = 2,8$  Hz; 4,9 Hz; 11,7 Hz; 46,9 Hz).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  em ppm (NMR spectra available in supporting information): 19,5 ( $\text{C}_5$ ), 27,0 ( $\text{C}_3$ ), 27,5 ( $\text{C}_8$ ), 29,7 ( $\text{C}_6$ ), 32,4 ( $\text{C}_7$ ), 46,1 ( $\text{C}_4$ ), 67,0 ( $\text{C}_1$ ), 94,7 ( $\text{C}_2$ ).

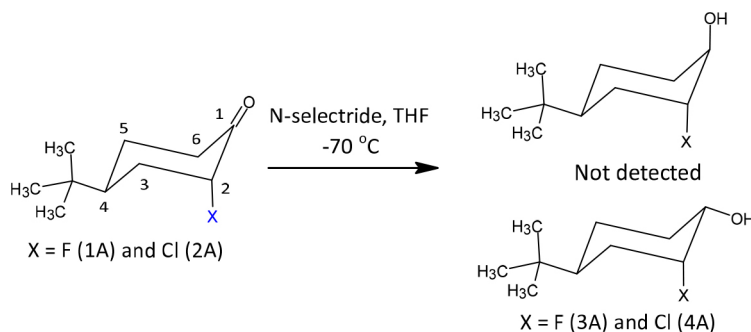
**4E:**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  in ppm (NMR spectra available in supporting information): 0,87 (9H,  $\text{H}_8$ , s), 1,13 (1H,  $\text{H}_{4\text{ax}}$ , m), 1,45 (3H), 1,75 (1H,  $\text{H}_{5\text{ax}}$ , m), 1,93 (1H,  $\text{H}_{5\text{eq}}$ , m), 2,20 (1H,  $\text{H}_{6\text{eq}}$ , m), 3,99 (1H,  $\text{H}_{1\text{eq}}$ , m), 4,07 (1H,  $\text{H}_{2\text{ax}}$ , ddd  $J = 2,5$  Hz; 4,5 Hz; 12,2 Hz).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 62,5 MHz)  $\delta$  in ppm (NMR spectra available in supporting information): 19,2 ( $\text{C}_5$ ), 27,5 ( $\text{C}_3$ ), 31,5 ( $\text{C}_8$ ), 31,7 ( $\text{C}_6$ ), 32,7 ( $\text{C}_7$ ), 48,5 ( $\text{C}_4$ ), 66,3 ( $\text{C}_1$ ), 68,9 ( $\text{C}_2$ ).

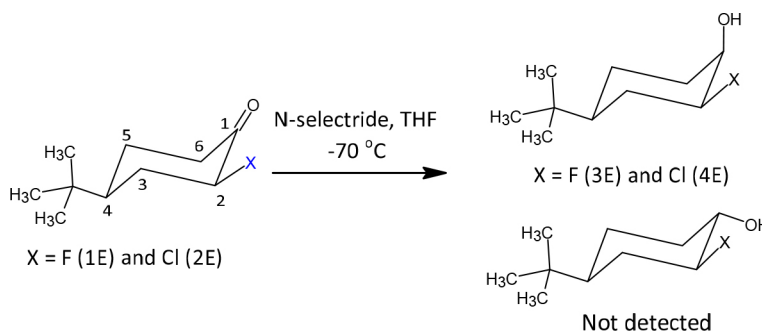
### 3. Results and discussions

#### 3.1. Diastereoselective of *trans* 4-*tert*-butyl-2-X-cyclohexanone (X=F and Cl)

In the reduction reaction of 1A and 2A, of 4-*tert*-butyl-2-X-cyclohexanone (X=F and Cl) isomers by reducing reactant



**Figure 3.** Reaction between the ketone, 1A and 2A, with reducing reactant N-selectride

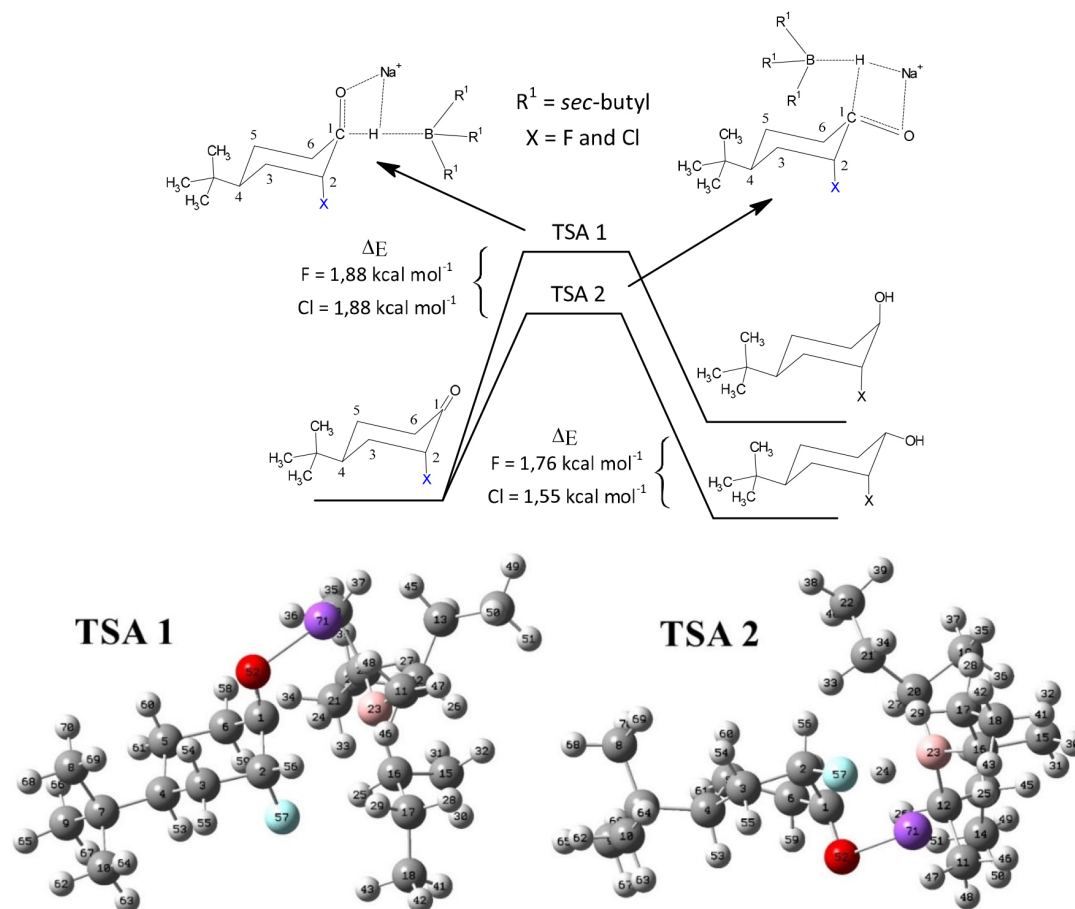


**Figure 4.** Reaction between the ketone, 1E and 2E, with reducing reactant N-selectride

N-selectride was obtained the *equatorial* alcohol 4-*tert*-butyl-2-X-cyclohexan-1-ol (Figure 5). Therefore, in this case was not obtained in detectable amounts of *axial* alcohol, that according with literature<sup>23</sup> this product is obtained with higher amounts in the reduction of 4-*tert*-butyl-cyclohexanone. To rationalize these experimental results was made theoretical calculations of transition state to evaluate whether the attack of nucleophile is favorable by *axial* face or *equatorial* face of carbonyl group. These calculations show that to 1A and 2A isomers the approximation of

N-selectride occur rather *axial* than *equatorial* face, because it leads to transition state **TSA 2** that is more stable than **TSA 1** of 1.88 and 1.94 kcal mol<sup>-1</sup>. These theoretical results are consistent with experimental dates (Figure 5).

We can use to explain the diastereoselective considering the steric repulsive interactions. In Table 1 are the main steric repulsive interactions considering the results of NBO analysis. The repulsion between the ketone and N-selectride, in transition state, is lower in **TSA 1** by 20.54 kcal mol<sup>-1</sup> to chlorine derivative and 24.48 kcal mol<sup>-1</sup> to fluorine derivative.



**Figure 5.** Reaction Path in reduction of *trans*-4-*tert*-butyl-2-x-cyclohexanone (X=F and Cl) and Transition state of reduction reaction of *trans*-4-*tert*-butyl-2-x-cyclohexanone with N-selectride in the attack by *equatorial* face (**TSA1**) and *axial* face (**TSA2**)

**Table 1.** Energies (kcal mol<sup>-1</sup>) for the most important repulsive steric interactions for transition state **TSA 1** and **TSA 2** calculated at the B3LYP/cc-pVDZ level

Interaction	TSA 1		Interaction	TSA 2	
	F	Cl		F	Cl
$\sigma_{B23-C12} \rightarrow \sigma_{C1-H24}$	10.3	10.1	$\sigma_{B23-H24} \rightarrow \sigma_{C1-C2}$	-	14.6
$\sigma_{B23-C16} \rightarrow \sigma_{C1-H24}$	11.5	11.7	$\sigma_{B23-H24} \rightarrow \sigma_{C1-C6}$	-	12.7
$\sigma_{C1-H24} \rightarrow \sigma_{C1-H24}$	9.7	9.3	$\sigma_{B23-H24} \rightarrow LP_{30}$	-	12.7
$\sigma_{C1-H24} \rightarrow \sigma_{C20-H27}$	3.0	3.1	$\sigma_{C21-H33} \rightarrow \sigma_{C2-H56}$	2.9	2.6
$\sigma_{C1-H24} \rightarrow \sigma_{C15-C16}$	2.4	2.6	$\sigma_{C11-H47} \rightarrow LP_{20}$	1.9	-
			$\sigma_{C11-H47} \rightarrow LP_{10}$	-	2.1
			$\sigma_{C11-H47} \rightarrow \pi_{C1-O}$	1.5	-
			$\sigma_{C21-H33} \rightarrow \sigma_{C6-H58}$	-	1.6

Therefore, the repulsive interactions further the transition state **TSA 1** for all ketones that yield the *equatorial* alcohol. This product was not observed, and steric repulsive interactions do not explain the experimental results.

The diastereoselective observed can be explained by Felkin-Ahn theory, which predicts that the bond vicinal to the reaction center which contained strongest electron withdrawing group, C<sub>2</sub>-X, should lie antiperiplanar to the incipient bond in order to maximize the orbital interaction  $\sigma_{C...Nu} \rightarrow \sigma_{C-X}^*$  in transition state. However, how can be observed in the structures of transition state obtained by calculations in figure 5, to the transition state **TSA2**, the ring bears a torsion, and the substituent takes a pseudo-*equatorial* position. This results in the loss of symmetry between the orbitals  $\sigma_{C...Nu}$  and  $\sigma_{C-X}^*$  and the orbital interaction  $\sigma_{C...Nu} \rightarrow \sigma_{C-X}^*$  is not possible in transition state. Seeing the Cieplak Model, that founded the strongest electron donation group should lie antiperiplanar to the incipient bond in order to maximize the  $\sigma_{C-X} \rightarrow \sigma_{C...Nu}^*$  orbital interaction in transition state, the experimental results is consistent with this theory, because in the torsion ring in **TSA 2** can occur the interaction  $\sigma_{C-C} \rightarrow \sigma_{C...Nu}^*$  that is more favorable, because the  $\sigma_{C-C}$  orbital is better donor of electrons than  $\sigma_{C-F}$  and  $\sigma_{C-Cl}$ .

Another factor that can influenced the diastereoselective observed is the torsion in some angles in transition state. We can observe, in **TSA 2**, the angle that suffer the higher torsion from ketone *trans 4-tert-butyl-2-X-cyclohexanone* is C<sub>2</sub>-C<sub>1</sub>-O, how show the table 2. But this torsion approaches the substituent (F and Cl) of metal making it possible electrostatic interaction between the metal positively charge and the substituent that has charge negative density. The energy of this electrostatic interaction supports the torsion energy that the ring suffers.

In transition state **TSA 1** the carbonyl group occupied an *axial* position. In this structure there is a higher torsion in angle C<sub>2</sub>-C<sub>1</sub>-O and C<sub>6</sub>-C<sub>1</sub>-O than **TSA 2** (entries 4 and 5 in Table 2). These differences become the fragment of carbonyl highly stressed in **TSA 1**, because the angle observed from the calculations (112.39 – 114.63° to C<sub>2</sub>-C<sub>1</sub>-O and 117.15 – 117.62° to C<sub>6</sub>-C<sub>1</sub>-O) is far from that to sp<sup>2</sup> carbon in ketone (120.48-121.22° to C<sub>2</sub>-C<sub>1</sub>-O and 124.05 – 124.63° to C<sub>6</sub>-C<sub>1</sub>-O), contributing to less stability for this transition state. The changes of other angles are close to both structures.

For the reduction reaction of *trans 4-tert-butyl-2-X-cyclohexanone* (X=F and Cl) a set of factors was analyzed to

explain the reduction reaction, that can further the reaction path through the TSA 2 transition state. We can conclude that the ring torsion makes the interaction  $\sigma_{C-C} \rightarrow \sigma_{C...Nu}^*$  possible to TSA 2, and the higher torsion in angle C<sub>2</sub>-C<sub>1</sub>-O and C<sub>6</sub>-C<sub>1</sub>-O to TSA 1 predict the diastereoselective observed to *trans-4-tert-butyl-2-fluoro-cyclohexanone*.

### 3.2. Diastereoselective of *cis 4-tert-butyl-2-X-cyclohexanone* (X=F and Cl)

In the case of substituent taking the *equatorial* position in the ketone, the experimental results showed that the reduction of 1E and 2E were obtained the alcohol with the hydroxyl group in *axial* position. Calculations show that the transition state that leads to this product due to the attack by N-selectride in the *equatorial* face (**TSE 1**, Figure 4) of the carbonyl group is more stable by 8.00 and 8.30 kcal mol<sup>-1</sup>. The energy of *axial* alcohol for all substituents are higher than *equatorial* alcohol. Therefore, in reduction reaction of 1E and 2E are obtained the kinetic product (Figure 6) because it is formed from the transition state more stable.

Relative to electronic effects, the Cieplak model is not consistent with experimental results, because the  $\sigma_{C-C} \rightarrow \sigma_{C...Nu}^*$  interaction that occur in **TSE 1** is less effective than  $\sigma_{C-H} \rightarrow \sigma_{C...Nu}^*$  interaction that occur in **TSE 2**, because the  $\sigma_{C-H}$  is better donor of electrons than  $\sigma_{C-C}$ .<sup>38</sup> By the model of Felkin-Ahn, we can be observe in the structures of transition state obtained by calculations that there is not a antiperiplanar symmetry to maximize the orbital interaction  $\sigma_{C...Nu} \rightarrow \sigma_{C-X}^*$ .

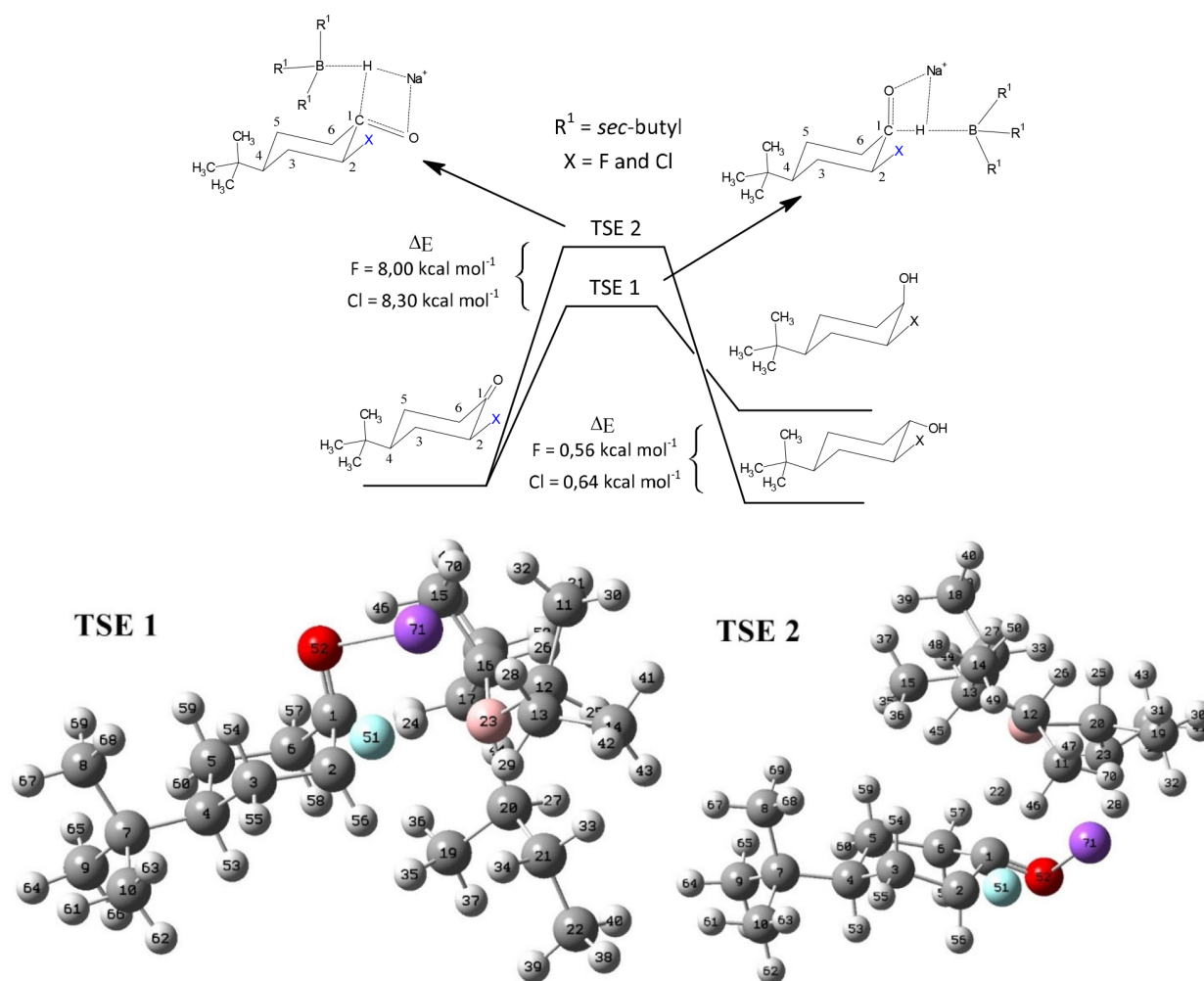
In table 3 are showed the main steric repulsive interactions considering the results of NBO analysis<sup>39</sup>. The repulsion between the ketone and N-selectride is lower in **TSE 2** by 0.95 kcal mol<sup>-1</sup> to chlorine derivative and 4.92 kcal mol<sup>-1</sup> to fluorine derivative. Therefore, these interactions cannot be used to explain the diastereoselectivity in reduction of *cis-4-tert-butyl-2-x-cyclohexanone* (X=F and Cl), because further **TSE 2** transition state.

In transition state **TSE 1** and **TSE 2** (Figure 6), the carbonyl group occupied *axial* and *equatorial* position, respectively, because in both structures occur a torsion in the ring on a carbonyl fragment. There is a higher torsion at angles C<sub>3</sub>-C<sub>2</sub>-C<sub>1</sub> and C<sub>5</sub>-C<sub>6</sub>-C<sub>1</sub> in **TSE 2** from the ketone *cis 4-tert-butyl-2-X-cyclohexanone* in fundamental state, as show the entries 1 and 2 in table 4. These differences cause the ring to be flattened in comparison with **TSE 1** and the

**Table 2.** bond angle for the transition state **TSA 1** and **TSA 2** and the ketones at fundamental state

Entry	Bond angle	TSA 1		TSA 2		Fundamental State	
		F	Cl	F	Cl	F	Cl
1	∠ C <sub>3</sub> -C <sub>2</sub> -C <sub>1</sub>	108.71	106.84	109.66	110.01	110.54	111.82
2	∠ C <sub>5</sub> -C <sub>6</sub> -C <sub>1</sub>	108.01	107.18	110.75	112.22	109.45	110.70
3	∠ C <sub>2</sub> -C <sub>1</sub> -C <sub>6</sub>	110.09	111.34	111.12	109.99	113.95	115.33
4	∠ C <sub>2</sub> -C <sub>1</sub> -O	114.63	112.39	116.35	117.56	121.22	120.48
5	∠ C <sub>6</sub> -C <sub>1</sub> -O	117.62	117.15	119.53	118.05	124.63	124.05





**Figure 6.** Reaction Path in reduction of *cis*-4-*tert*-butyl-2-x-cyclohexanone (X=F and Cl) and Transition state of reduction reaction of *cis*-4-*tert*-butyl-2-x-cyclohexanone with N-selectride in the attack by *equatorial* face (TSE1) and *axial* face (TSE2)

**Table 3.** Energies (kcal mol<sup>-1</sup>) for the most important repulsive steric interactions for transition state **TSE 1** and **TSE 2** calculated at the B3LYP/cc-pVDZ level.

Interaction	TSE 1		Interaction	TSE 2	
	F	Cl		F	Cl
$\sigma_{B23-C12} \rightarrow \sigma_{C1-H24}$	8.3	7.4	$\sigma_{B23-C20} \rightarrow \sigma_{C1-H22}$	8.8	9.2
$\sigma_{B23-C16} \rightarrow \sigma_{C1-H24}$	11.2	9.7	$\sigma_{B23-C12} \rightarrow \sigma_{C1-H22}$	7.1	6.2
$\sigma_{B23-C16} \rightarrow \sigma_{C1-H24}$	9.6	8.6	$\sigma_{B23-C12} \rightarrow \sigma_{C1-H22}$	7.1	7.4
$\sigma_{C1-H24} \rightarrow \sigma_{C12-H25}$	2.4	2.4	$\sigma_{C20-H25} \rightarrow \sigma_{C1-H22}$	2.3	2.6
$\sigma_{C1-H24} \rightarrow \sigma_{C16-H26}$	2.5	2.4	$\sigma_{C16-H33} \rightarrow \sigma_{C1-H22}$	2.4	2.4
$\sigma_{C1-H24} \rightarrow \sigma_{C20-H27}$	2.3	2.3	$\sigma_{C12-H36} \rightarrow \sigma_{C1-H22}$	2.5	2.7
			$\sigma_{C23-H28} \rightarrow LP_{(1)}O$	3.0	1.5
			$\sigma_{C23-H29} \rightarrow \sigma_{C6-H57}$	0.5	2.6
			$\sigma_{C15-H35} \rightarrow \sigma_{C5-H59}$	4.1	3.7

consequence of this are that the carbons 2 and 6 become highly stressed in **TSE 2**, because the angle observed from the calculations ( $117.07 - 117.39^\circ$  to  $C_3-C_2-C_1$  and  $117.60$  and  $118.40^\circ$  to  $C_5-C_6-C_1$ ) is far from of angle to  $sp^2$  carbon in ketone ( $110.86-110.99^\circ$  to  $C_3-C_2-C_1$  and  $111.49$  and  $111.32^\circ$  to  $C_5-C_6-C_1$ ) contributing to less stability for this

transition state. The changes of other angles are close to both structures.

Besides the higher ring torsion angle to TSE 1 than TSE 2 (Table 3) can be used to elucidate the diastereoselective in reduction reaction of *cis* 4-*tert*-butyl-2-X-cyclohexanone (X=F and Cl).

**Table 4.** bond angle for the transition state **TSE 1** and **TSE 2** and the ketones at fundamental state

Entry	Bond angle	TSE 1		TSE 2		Fundamental State	
		F	Cl	F	Cl	F	Cl
1	$\angle C_3-C_2-C_1$	109.74	110.01	117.07	117.39	110.99	110.86
2	$\angle C_5-C_6-C_1$	108.01	109.38	117.60	118.40	111.32	111.49
3	$\angle C_2-C_1-C_6$	109.50	108.12	110.52	109.36	113.08	112.39
4	$\angle C_2-C_1-O$	115.85	116.99	114.49	116.17	122.94	124.32
5	$\angle C_6-C_1-O$	116.86	116.36	117.04	115.40	123.95	123.28

## 4. Conclusion

The reduction reaction of 4-*tert*-butyl-2-X-cyclohexanone (X=F and Cl) with N-selectride was studied by experimental results and theoretical calculations and was observed that the substituents in *axial* position provide the *equatorial* alcohol. Calculations of transition state is consistent with these experimental results because the **TSA 1** (attack by *axial* face) is more stable than **TSA 2** (attack by *equatorial* face). We use the Cieplak model and energy torsion for explain these results. However, with the substituents in *equatorial* position was formed the *axial* alcohol and our calculations show that is the kinetic product. Calculations of transition state show that **TSE 1** (attack by *equatorial* face) is more stable than **TSE 2** (attack by *axial* face). The torsion of angles in ring may the factors that lead the lower energy in **TSE 1**.

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