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Understanding the cyclization step for the preparation of pseudopeptidic macrocycles. Optimization of the process trough a theoretical analysis

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Abstract

The influence of the pH and the effect of the chloride as catalyst on the activation barrier for the cyclization of a C_2 pseudopeptide with 1,3-bis(chloromethyl)benzene reaction has been studied theoretically. For this purpose all the stationary points were fully optimized with the B3LYP/6-31G level of theory. A frequency calculation was performed for each stationary point. The vibrational analysis was carried out for each structure and the Gibbs Energy was therefore calculated. The activation barrier of the cyclization step was obtained from these calculations. Data obtained show that in the transition state the anion Cl^- is coordinated with the H atom of one amine and the H atom of one amide functionality and this arrangement reduces the activation energy of the cyclization reaction. From the different calculated energy barriers for the alternative reaction pathways studied, the lowest one is calculated for occur for the reaction catalysed by one chloride and with both amine groups not protonated. Those conditions have been checked experimentally to be the optimal for the process to occur.

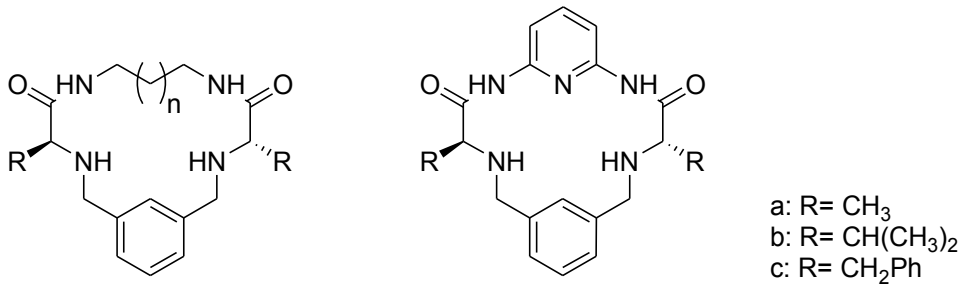
Introduction

Pseudopeptidic compounds have applications in different research areas. These compounds derived from aminoacids and containing non-natural structural components, are very often good abiotic receptors. The presence of donor nitrogen atoms from amino groups provide coordination properties toward metal centers while they can bind efficiently anions when protonated and taking advantage of the presence of the amide NH group. In this regard they can be even used as anion enantioselective receptors.[1] On the other hand, nitrogen atoms can be transformed into a variety

of functionalities such as ammonium, amide, urea, thiourea, guanidine or pyrrol group. [2] In recent years our group has been involved in the preparation and study of different macrocyclic pseudopeptides.[3] In the present work we have studied, using theoretical tools, some of those macrocyclizations starting from C_2-open chain pseudopeptides derived from diamines. The results obtained allow to better rationalize the experimental results and to open new strategies for the optimization of those processes.

Previous studies of our group had focused on macrocyclic structures like **1**.[3] In order to introduce further functionalities in the system, we consider the preparation of macrocyles **2**. Initial experiments for the preparation of **2b** and **2c** revealed soon that the corresponding macrocyclization is more difficult than observed for **1**.

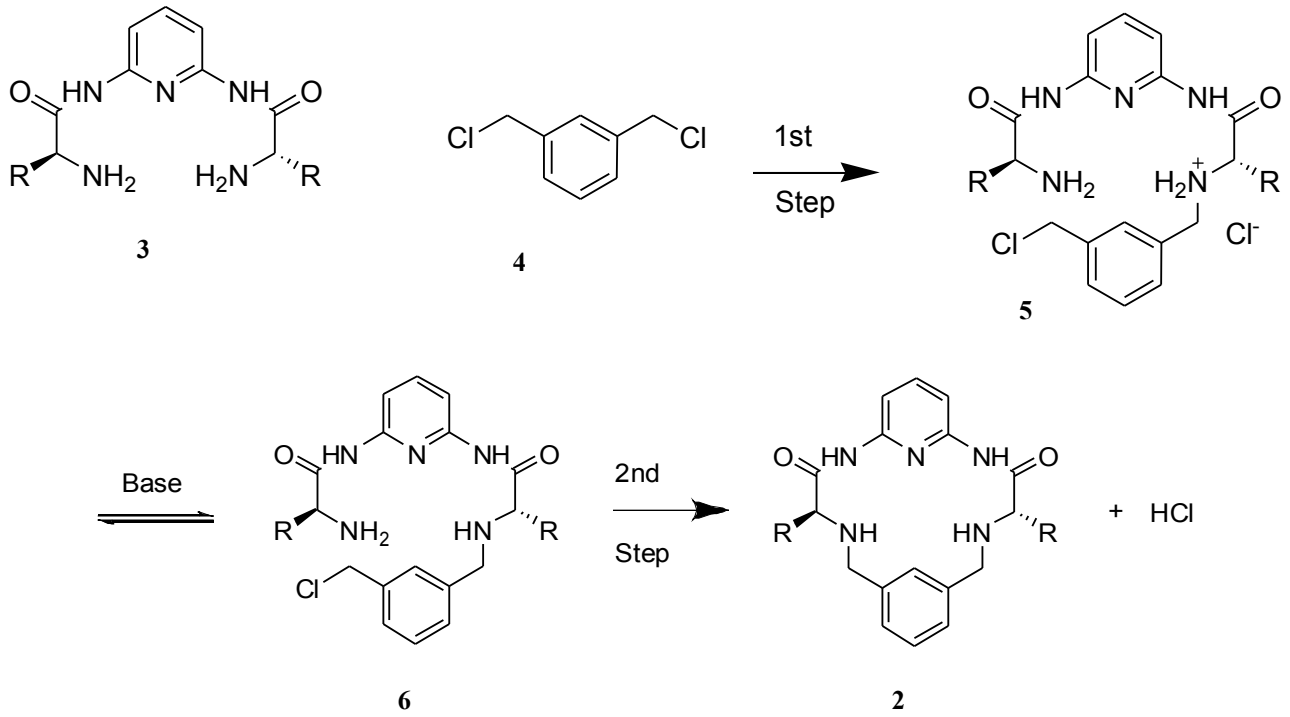
Thus, we carried out a theoretical study in order to better understand this process and to obtain some insights into novel strategies that could allow us to improve this synthetic procedure. The alanine derivative **2a** was chosen as the model system. This reduces the number of atoms in comparison to **2b** and **2c**, and, accordingly, the calculation time. Moreover, this avoids the need for performing the conformational analyses associated to the side chain.



1 **2**

Chart 1: Macrocycles studied

The synthetic procedure for the synthesis of macrocyles **1** and **2** must take place in two steps (see Scheme 1). In the first step, one of the C-N bonds is formed through an intermolecular S_N2 reaction. This is accompanied by the formation of one equivalent of acid. The acid formed must be neutralized by a base present in the reaction medium.



Scheme 1.

The role of the base added (i.e. CO_3^{2-}, triethylamine) is important, not only to avoid protonation of intermdiate **6** that could difficult the second step and lead to the reversal of the process, but also to prevent the protonation of the unreacted diamine **3** leading to a less reactive initial reagent. Therefore, the control of the acidity of the medium is important for this reaction. The second step is the macrocyclization reaction, and again it requires neutralization of the acid formed. This is the rate limiting step and therefore, the activation barrier for this process needs to be studied as the energetic barrier for the overall reaction (from **3** to **2**).

The general representation of the transition state for this cyclization step can be schematized as shown in Figure 1a. Some additional variables can be considered for the corresponding TS. Thus it seems reasonable to assume that the presence of a relatively basic anion such as Cl^- coordinated to one of the H atoms of the reacting amino group (Figure 1b) could reduce the energy of the corresponding TS and act as an efficient catalyst for this step. Alternative TSs can also be drawn considering the cyclization process starting not from a neutral intermediate **6** (TSs of Figure 1a and Figure 1b) but from the intermediate **5** having a protonated secondary amino groups.

The main objective for this study has been to understand the macrocyclization mechanism and how

the activation barrier can be modified by the presence of chloride anions and by the protonation of the secondary amino groups in the open-chain intermediate (**5** or **6**).

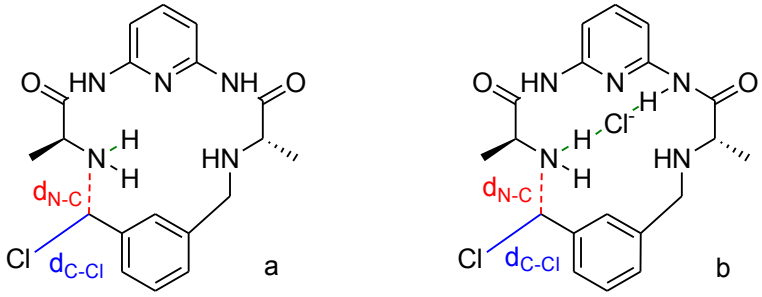


Figure 1: Proposed Transitions States of the macrocyclization step

Computational methods

The structure of the reactants, the complex resulting of the interaction of reactants (RIC), the transition state (TS), the complex for the interaction of products (PIC) and the products were fully optimized in order to obtain the whole reaction profile (Figure 2).

The geometry of each stationary point was optimized at the B3LYP level with the 6-31G basis set. [4] We selected this basis set because it allows us to perform the calculations in a reasonable calculation time taking into consideration the complexity of this and related systems. The use of more elaborated basis sets require the use of prohibitive calculation times. All the calculations have been performed with the program Gaussian 03.[4] Stationary points were confirmed by vibrational analysis. For equilibrium structures (reactants, RIC, TS, PIC and products), all normal modes have real frequencies. For transition states, they only have one normal mode with an imaginary frequency, and this frequency is associated to the vibration of the bonds that are formed and broken. Furthermore, transition states were verified to connect the reactants and products by carrying out intrinsic reaction coordinate (IRC) calculations.

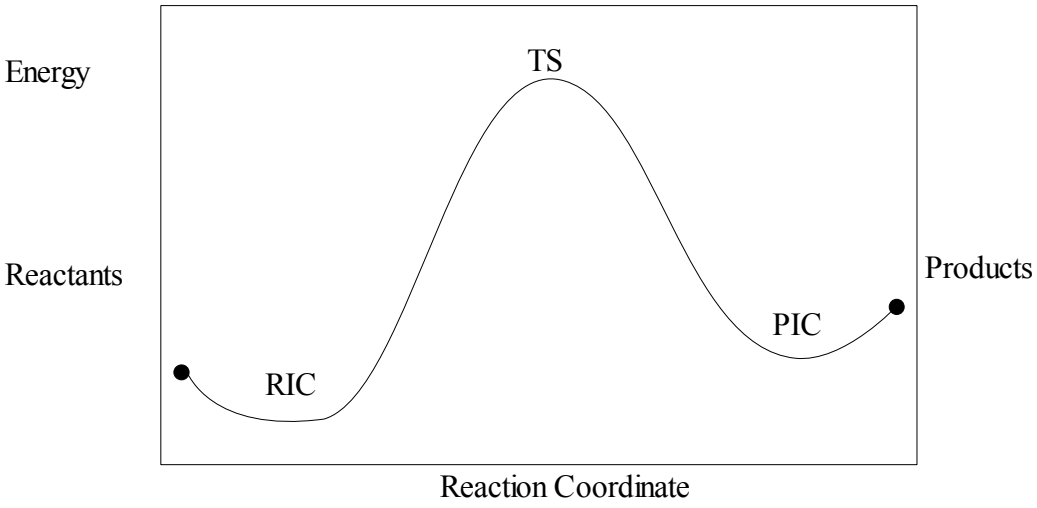


Figure 2: Schematic representation of a reaction profile.

Results and discussion

The calculations were carried out for the four alternative reaction profiles related to the presence or absence of coordinated chloride anions and the presence of protonated or non-protonated secondary amino groups (open chain intermediates **5** or **6**):

Pathway 1: Non protonated secondary amino groups; absence of chloride catalyst ($0H^+$,$0Cl^-$)

Pathway 2: Non protonated secondary amino groups; presence of one chloride catalyst ($0H^+$,$1Cl^-$)

Pathway 3: Protonated secondary amino groups; presence of one chloride catalyst ($1H^+$,$1Cl^-$)

Pathway 4: Protonated secondary amino groups; presence of two chloride catalyst ($1H^+$,$2Cl^-$)

The study and comparison of these four reaction mechanisms can allow to analyse the influence of the pH and the effect of the chloride as a catalyst on the cyclization step. It is expected that the better experimental conditions to carry out the cyclization at the laboratory will correspond to those four which a lower activation energy (RIC-TS) is found be the calculations.

As seen in Scheme 1, the open-chain intermediates initially formed, having a protonated secondary

amino group and containing a chloride anion that can participate in further steps. According to this the study of the four reaction pathways for the rate limiting cyclization step is required.

Initially,we performed a Potential Energy Surface Scan (PES) at the PM3 level in order to see the different energy profiles and to reduce the calculation time in comparison to the B3LYP/6-31G method. Figure 3 shows how the PES depend on the reaction pathway considered.

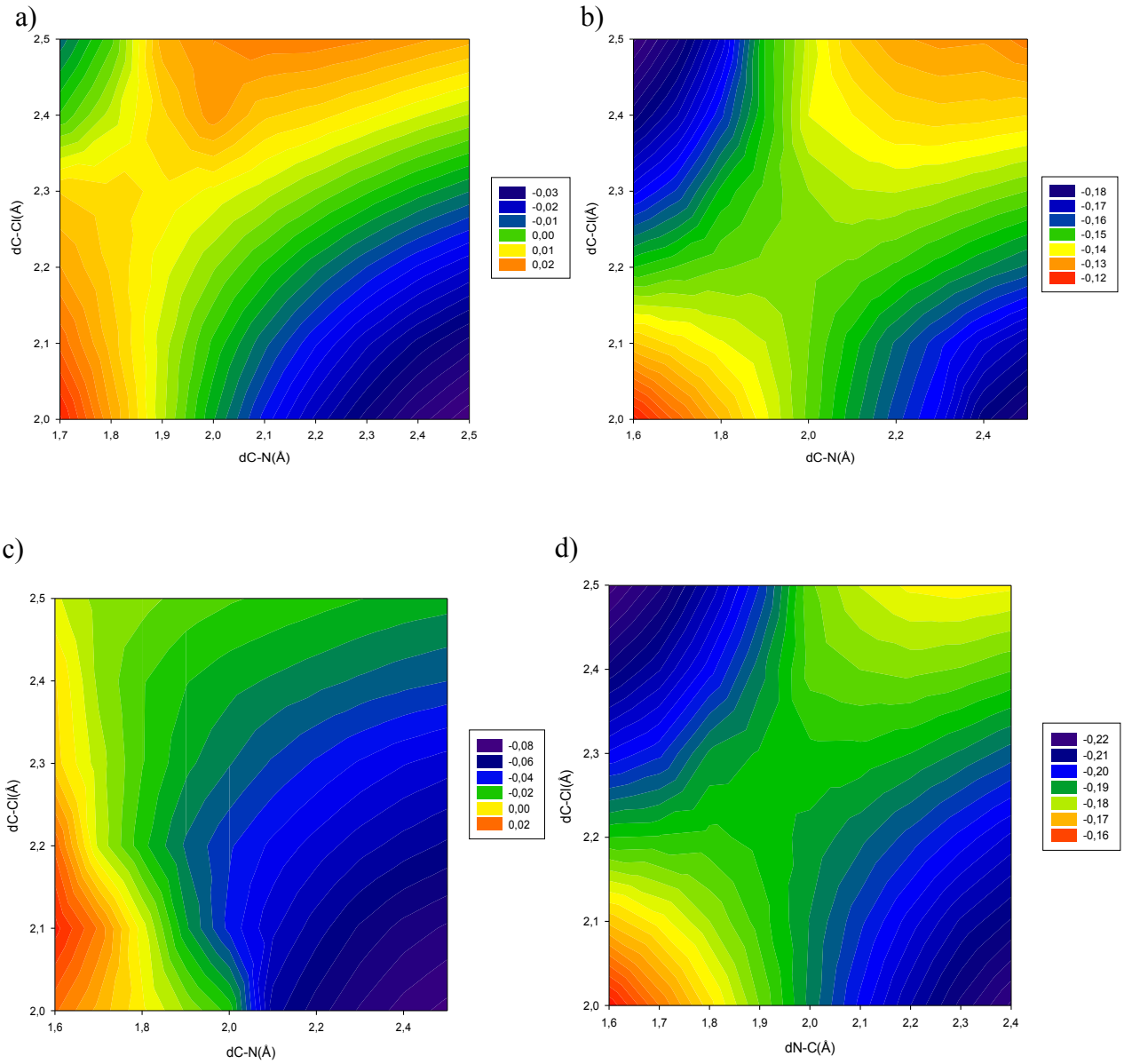


Figure 3: PES for the four reaction profiles (PM3 Energy in Hartrees) for the cyclization reaction of 1,3-bis(chloromethyl)benzene a) unprotonated secondary amino groups and without catalyst. b) unprotonated secondary amino groups and Cl^- as a catalyst c) protonated secondary amino groups and catalysed by 1 Cl^-. d) protonated secondary amino groups and catalysed by 2 Cl^-.

The calculations on the different energy profiles can allow obtaining the different activation barriers for the cyclization reaction. The Figure 4 shows the calculated transition states for the different pathways fully optimized with the B3LYP/3-61G level of theory. We can see the coordination of the catalyst (chlorine atom) with the hydrogens of the nitrogen groups of the macrocycle in the Figure 4 b, c and d .

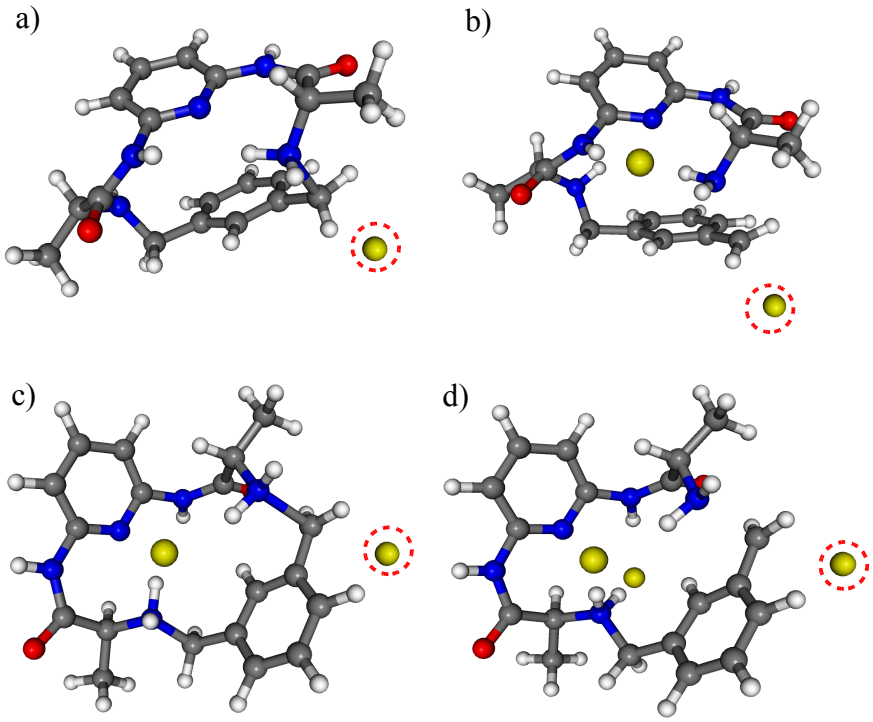


Figure 4: Possible Transition States (fully optimized with the B3LYP/3-61G level of theory) for the cyclization reaction of 1,3-bis(chloromethyl)benzene a) unprotonated secondary amino groups and without catalyst. b) unprotonated secondary amino groups and Cl^- as a catalyst c) protonated secondary amino groups and catalysed by 1 Cl^-. d) protonated secondary amino groups and catalysed by 2 Cl^-. Chlorine: yellow; nitrogen: blue; oxygen: red; carbon: grey; hydrogen: white. The encircled chlorine atom is the leaving group, the other chlorine atoms correspond to the chloride anions.

The distances of the bonds that are formed and broken in the S_N2 reaction (see Figure 1) for the limiting step depend on the reaction pathway. This clearly are shown in the Table 1, where the values obtained are significantly dependent of the pathway selected.

Table 1: Distances in the Transtion States calculated with the B3LYP/3-61G level of theory

Distance (Å)	0H$^+$, 0 Cl$^-$	0 H$^+$, 1 Cl$^-$	1 H$^+$, 1 Cl$^-$	1 H$^+$, 2 Cl$^-$
dC-Cl	2.621	2.423	2.623	2.600
dC-N	1.922	2.202	1.931	2.061

On the one hand, the presence of a catalytic Cl$^-$ anion coordinating to one H atom of the nucleophilic hydrogen significantly decreases the C-Cl distance and increases the C-N distance. On the other hand, the protonation increases the C-Cl distance and decreases the one for C-N. This effect can be explained because the anion stabilizes the positive charge that is formed over the nitrogen as the reaction takes place.

Table 2 gathers the Gibbs energies calculated for each stationary point. The representation of the corresponding reaction profiles is shown in Figure 5.

Table 2: Relative Gibbs Free Energy (B3LYP/3-61G) in kcal/mol for the cyclization reaction for the different energy profiles simulated.

	0H$^+$, 0 Cl$^-$	0 H$^+$, 1 Cl$^-$	1 H$^+$, 1 Cl$^-$	1 H$^+$, 2 Cl$^-$
Reagents	0.00	0.00	0.00	0.00
RIC	0.00	-21.74	-14.24	-45.29
TS	30.01	-7.52	18.94	-26.32
PIC	6.39	-29.69	-17.49	-58.85
Products	7.46	7.46	7.46	7.46

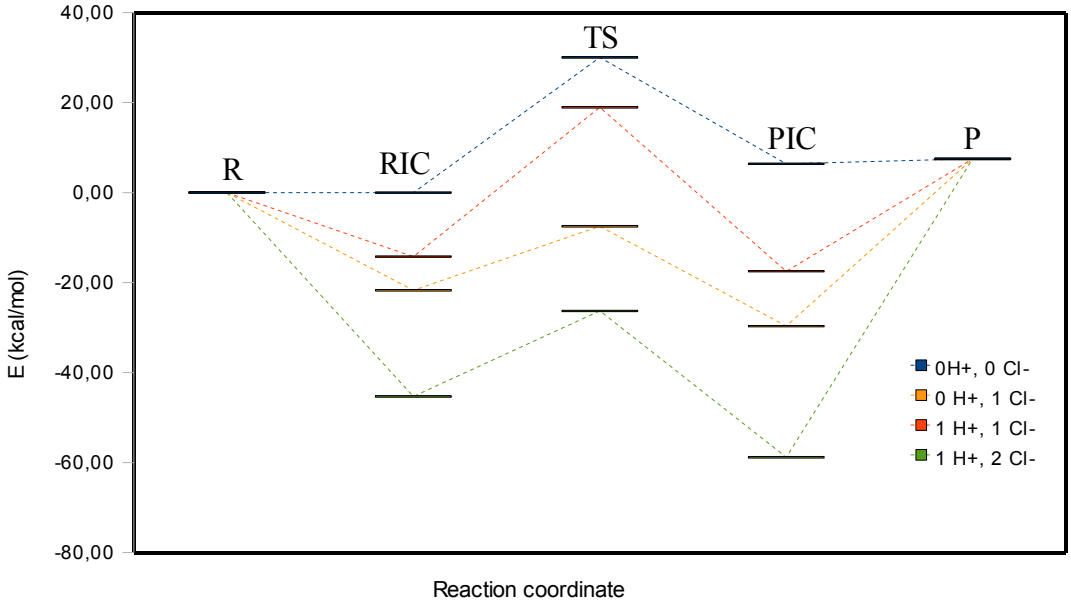


Figure 5: Gibbs Free Energy in kcal/mol for the cyclization reaction for the different energy profiles simulated.

From those data we can calculate the barriers between the stationary points. The most important one is the RIC-TS barrier, being the limiting barrier for the cyclization step (Table 3).

Table 3: Gibbs Free Energy (B3LYP/3-61G) activation barriers in kcal/mol for the cyclization reaction for the different energy profiles simulated.

	0H^+, 0 Cl^-	**0 H^+, 1 Cl^-**	**1 H^+, 1 Cl^-**	**1 H^+, 2 Cl^-**
Reactivos-RIC	0.00	-21.74	-14.24	-45.29
RIC-TS	30.01	14.22	33.19	18.97
TS-PIC	-23.63	-22.17	-36.43	-32.53
PIC-Productos	1.08	37.15	24.95	66.31

Those data suggest that the most favourable reaction profile is that taking place from the unprotonated open-chain intermediate **6** and with the presence of a Cl^- anion acting as a catalyst.

Conclusions

In conclusion, our results show that the protonation and the coordination of chloride have a definite effect on the activation energy for the cyclization reaction. This reaction has the lowest activation energy if the transition state is not protonated at the secondary amino group and one chlorine atom acts as catalyst. Therefore to improve this reaction the pH of the reaction medium must be basic to avoid the protonation. This leads to consider the use of amines as the base and chloride anion as the catalyst. This suggests a simple experimental set-up to accomplish those conditions should be using chloride tetrabuthylammonium salt (TBACl) as the Cl^- source and triethylamine as a base in the reaction medium. Experimental results confirm that the reaction is much more effective under those conditions.

References

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