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A computational study of regioselectivity in β-lactam iminothiazolidinone formation

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ABSTRACT

Density functional theory calculations were performed to explain the different regioselectivity for the formation of β-lactam iminothiazolidinones. Computational results were in agreement with experimental observations that phenyl and cyclohexyl derivatives led to the thermodynamically more stable regioisomers formed by cyclization at the nitrogen atom directly attached to the β-lactam ring which was in contrast to the *n*-hexyl derivative where the regioisomer with the β-lactam ring attached to the imino bond is more stable instead. It was demonstrated that the different regioselectivity was the consequence of larger steric effects when bulky substituents and the leaving ethoxy group were in close contact during the cyclization step.

Introduction

The β-lactam unit is one of the key synthons in the preparation of novel molecular scaffolds.[1] This motif plays an important role in delivering chiral information in the asymmetric synthesis of compounds[1,2] as well as providing a useful route to different heterocycles.[1,3,4] Besides being crucial for the activity of biologically active compounds such as antibiotics[5] and cholesterol absorption inhibitors,[6] it is also vital for the synthesis of various amino acids, peptides, and nitrogen containing poly-functional molecules.[7]

The preparation of five membered iminothiazolidinones by the reaction of thioureas and α-haloalkanoic acids (or their derivatives) has been previously reported in the literature.[8–11] Experimental evidence has shown for the preparation of iminothiazolidinones from non-symmetrical thioureas, two regioisomers are formed depending on the nitrogen atom involved in the cyclization and formation of the five-membered ring. In most cases, one regioisomer predominates and is dependent on the electronic properties of the starting thiourea substituents. When the starting thiourea bears substituents with similar electronic properties, the product regioselectivity is minimal.[8–11]

As part of our own synthetic efforts to broaden the versatility of this reaction,[12,13] we have investigated the preparation of variously substituted β-lactam iminothiazolidinones.[14] This investigation demonstrated an iminothiazolidinone regioselectivity which could not be fully explained by known mechanistic details[8–11] since chemically different thiourea substituents mostly led to structurally equivalent regioisomers, regardless of their electronic properties.[14] However, in the case of an *n*-alkyl substituent, the regioisomer with a different structural arrangement was isolated in excess. This unusual regioselectivity pattern prompted us to perform a more detailed mechanistic analysis of the reaction mechanism, by employing a detailed quantum-chemical analysis. Herein, we propose a reaction pathway which reveals an interesting interplay of electronic and, more importantly, steric factors leading to the observed regioselectivity.

Results and discussion

We began with the synthesis of amino-β-lactam **1** according to known methods.[15,16] The treatment of amino-β-lactam **1** with the corresponding isothiocyanates in CH_3CN at RT resulted in the formation of β-lactam thioureas **2a–i**.[14] Thioureas **2a–i** were then subjected to condensation with ethyl-bromoacetate in the presence of 2.0 equiv of Na_2CO_3 to give β-lactam iminothiazolidinones **3a–i/i′** in good yields[14] (Scheme 1).

In the case of β-lactam substituted thioureas **2a–i** (Table 1) the cyclization reaction gave only one iminothiazolidinone regioisomer **3a–h**, except in the case of the *n*-hexyl substituted thiourea **2i** which afforded iminothiazolidinones **3i/i′** which were isolated

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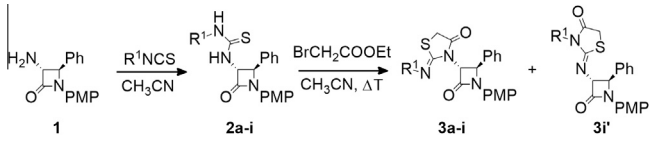
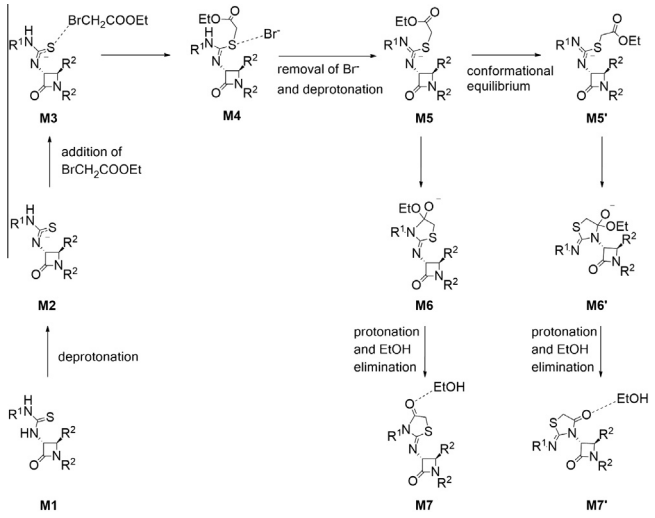


Scheme 1. Synthesis of β-lactam iminothiazolidinones **3a**–**i**/**3i′**.



Scheme 2. Model representation of the regioselective iminothiazolidinone formation mechanism. R^1 = phenyl, cyclohexyl, *n*-hexyl; R^2 = methyl.

Table 1
Experimental yields of β-lactam thioureas **2a**–**i** and iminothiazolidinones **3a**–**i**/**3i′**

	R^1	Yield of **2** (%)	Yield of **3** (%)
a	Ph	96	73
b	*p*-NO_2Ph	81	96
c	2-ClPh	94	92
d	2-FPh	66	90
e	*p*-N_3Ph	85	45
f	*p*-CNPh	97	84
g	Cy	72	77
h	Norbornyl	94	99
i	*n*-Hexyl	54	67 (**3i**:**3i′** = 23:77)[a]

[a] Two regioisomers are formed and their ratio is determined by NMR and HPLC analysis.

from the reaction mixture in a 23:77 ratio, as confirmed by NMR. In particular, it was interesting to see that the structures of iminothiazolidinones **3g** and **3h** bearing electron donating alkyl groups have the same structural arrangement as iminothiazolidinones **3a**–**f**, which contained aryl substituents that were stabilized by resonance.

In order to examine these findings in more detail, we chose phenyl, cyclohexyl, and *n*-hexyl substituents as models in subsequent density functional theory (DFT) calculations. Phenyl and cyclohexyl substituents were chosen due to the resonance stabilization effect (and lack of it, respectively) and their comparable sizes, whereas an *n*-hexyl substituent was selected due to its flexible acyclic structure in comparison to the rigid phenyl and cyclohexyl substituents.

Free energy barriers and protonation/deprotonation free energies are given in Table 2 while the energy diagram is schematically presented in Figure 1. In the first part of the mechanism, the reaction path starting from **M-1** and leading to **M-5** is identical for all R^1 substituents. Initially, deprotonation of the starting compound

Table 2
Free energy differences ΔG in kcal mol^{-1} between selected steps along the reaction mechanism (Scheme 2) calculated at the SMD/B3LYP/6-311++G(2d,p)//B3LYP/6-31+G (d) level of theory

	Phenyl	Cyclohexyl	*n*-Hexyl
M-1	0.0	0.0	0.0
M-2	297.3	300.3	300.8
Complexation with $BrCH_2COOEt$			
M-3	0.0	0.0	0.0
M-TS_1[a]	8.5	6.6	7.1
M-4	−23.1	−23.7	−21.9
Elimination of Br^-			
M-5	0.0	0.0	0.0
M-TS_2[b]	14.2	14.6	10.5
M-6	−0.2	−2.6	−3.3
M-7	−319.4	−325.3	−322.4
Conformational change pathway			
M-5′[c]	2.8	2.0	3.4
M-TS_2′[d]	7.1	8.3	7.8
M-6′	0.2	−3.0	−2.6
M-7′	−318.0	−321.5	−321.9
$\Delta\Delta G$[e]	−2.5	−0.7	1.9

[a] Imaginary frequencies: 387*i* cm^{-1} (phenyl), 387*i* cm^{-1} (cyclohexyl), 382*i* cm^{-1} (*n*-hexyl).
[b] Imaginary frequencies: 124*i* cm^{-1} (phenyl), 188*i* cm^{-1} (cyclohexyl), 183*i* cm^{-1} (*n*-hexyl).
[c] Energy relative to **M-5**.
[d] Imaginary frequencies: 154*i* cm^{-1} (phenyl), 149*i* cm^{-1} (cyclohexyl), 154*i* cm^{-1} (*n*-hexyl).
[e] Free energy difference between products **M-7** and **M-7′**.

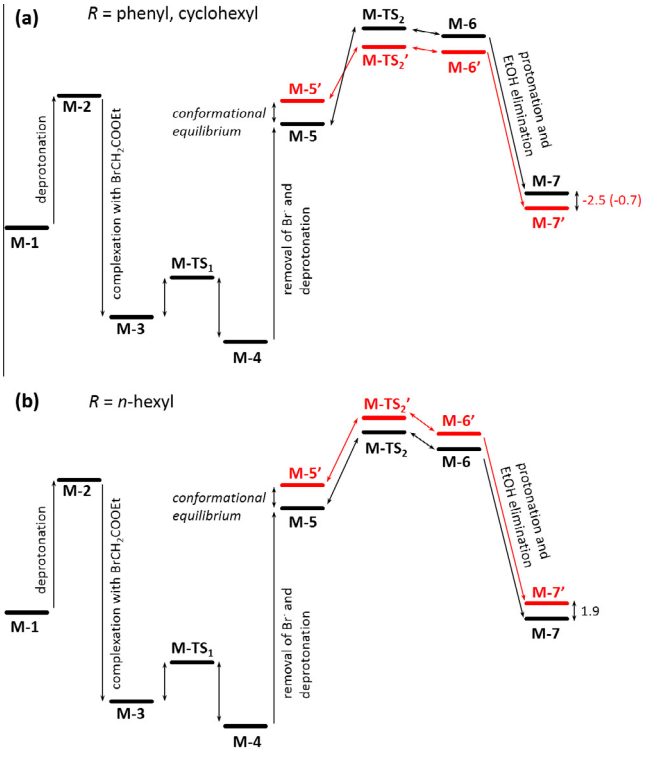


Figure 1. Schematic representation of energy diagrams in (a) phenyl, cyclohexyl and (b) *n*-hexyl derivatives of iminothiazolidinone. Free energy difference is given in kcal mol^{-1}.

M-1 with the first equivalent of Na_2CO_3 occurs, resulting in the formation of the anion **M-2**. Although in principle four conformers are possible in the case of **M-1**, only the most stable conformation (and in turn its anion **M-2**), were considered in further calculations. Upon deprotonation of the **M-2**, addition of ethyl-bromoacetate

($BrCH_2COOEt$) led to the formation of weakly bound complex **M-3**. Nucleophilic attack of the sulfur group to the electrophilic carbon atom in $BrCH_2COOEt$ resulted in the formation of compound **M-4**. This reaction is exergonic, as shown by the free energy barriers of 6–8 kcal mol^{-1} followed by stabilization of **M-4** by 22–24 kcal mol^{-1} (depending on the substituents). In order to follow the further reaction steps more easily, the Br^- anion was removed from complex **M-4** since it was not essential in the subsequent reaction steps.

After removal of Br^- anion from molecule **M-4** and deprotonation with a second equivalent of Na_2CO_3, **M-5** is formed which represents a branching point for regioselective reactions. The first possible pathway proceeds via direct nucleophilic attack of the nitrogen atom substituted with R^1 groups leading to **M-6**. In the case of phenyl and cyclohexyl groups, the calculated barrier for cyclization was around 14 kcal mol^{-1}, which contrasted with the *n*-hexyl group where the barrier was lowered by 4 kcal mol^{-1}. After cyclization, **M-6** is protonated in the reaction mixture leading to elimination of EtOH and the final product **M-7**. The second possible pathway involves cyclization of the nitrogen atom directly connected to the β-lactam ring. In order for this reaction to occur, an additional conformational change is necessary to position the reactive nitrogen and carbon centers in closer contact. Unfortunately, the barrier for the process could not be computationally determined due to the complex conformational change, but it was calculated that isomers **M-5′** were destabilized by 2–3 kcal mol^{-1} with respect to **M-5**. Regardless of this energetically slightly unfavorable step, in the cases of phenyl and cyclohexyl group the ensuing products **M-6′** were found to be more easily accessible when compared to the pathway without conformational change (7.1 and 8.3 kcal mol^{-1} versus 14.2 and 14.6 kcal mol^{-1}, respectively). Moreover, after protonation and elimination of EtOH, thermodynamically more stable products **M-7′** are obtained with energy differences compared to **M-7** being −2.5 and −0.7 kcal mol^{-1}, respectively. In the case of the *n*-hexyl group, regardless of the lower barrier leading to **M-6′** as compared to **M-6** (7.8 versus 10.5 kcal mol^{-1}, respectively), a thermodynamically less stable product was obtained with energy difference to **M-7** being +1.9 kcal mol^{-1}. These results were in agreement with the experimental data presented in Table 1 where **M-7′** was isolated in the case of phenyl and cyclohexyl substituent (compounds **3a** and **3g**) while in the case of *n*-hexyl substituent (compound **3i′**) **M-7** was isolated in excess. While the exact ratio of structural regioisomers could not be predicted based on the free energy differences between **M-7** and **M-7′**, it was gratifying to note that the regioselectivity pattern was reproduced with DFT calculations.

Next we explain the reasons for the different regioselectivities. In order to demonstrate this more clearly, the geometries of the relevant structures in the conversion of **M-5** to the regioisomer **M-6** formed by cyclization with the R^1-nitrogen atom (Fig. 2a) in the case of phenyl substituent were compared (geometries of the cyclohexyl derivatives are not shown due to a qualitatively similar picture). At the same time we also show the cyclization step leading to regioisomer **M-6′** formed by cyclization with the nitrogen atom directly attached to the β-lactam ring (Fig. 2b). It can be seen that product **M-6** is destabilized compared to the transition structure **M-TS$_2$** as reflected by a very long C–N bond of 1.64 Å. This was also visible in the relative energy of **M-6**, which is only 0.2 kcal mol^{-1} more stable than the transition state **M-TS$_1$** (Table 1). The same situation held true for product **M-6′** which is less stable (but only when thermal correction is taken into account, see ESI) than **M-TS$_2$′** by 0.2 kcal mol^{-1}, also having a relatively long C–N bond distance of 1.58 Å. Still, there are notable differences in these two cyclization steps, and it was determined that it was twice as expensive to bring the ethoxy and phenyl groups together (Fig. 2a) than the β-lactam ring and phenyl group, (Fig. 2b) as

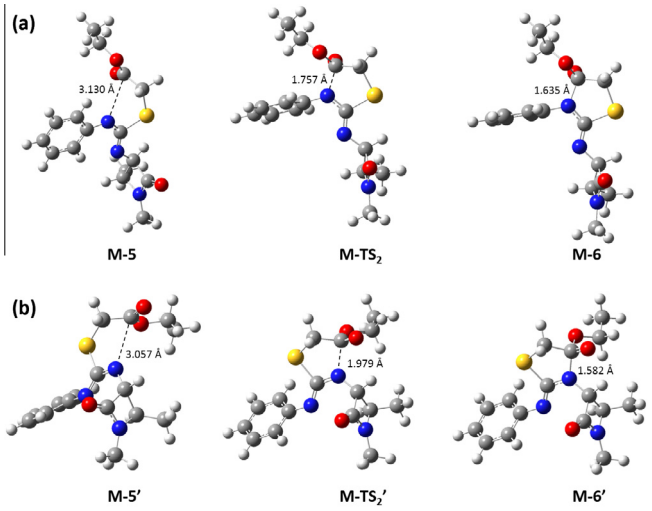


Figure 2. Optimized geometries during the five-membered ring cyclization step for phenyl derivatives of iminothiazolidinone. (a) Transformation from **M-5** to **M-6**; (b) transformation from **M-5′** to **M-6′** after conformational change of **M-5** to **M-5′**.

reflected by the calculated free energy barriers (14.2 kcal mol^{-1} versus 7.1 kcal mol^{-1}, respectively). Although both products **M-6** and **M-6′** are relatively unstable due to a negligible barrier for the reverse reaction, they are immediately protonated in the reaction mixture leading to the final products **M-7** and **M-7′**, where **M-7′** is 2.5 kcal mol^{-1} more stable than **M-7**. Therefore, the formation of **M-7′** is preferred both kinetically (due to steric reasons and in turn the lower free energy barrier for cyclization of **M-5′** to **M-6′**) and thermodynamically (as witnessed by the larger stability of product **M-7′**). A similar situation also held for cyclohexyl derivatives and the final product **M-7′** was 0.7 kcal mol^{-1} more stable than **M-7**. However, products **M-6** and **M-6′** were both slightly stabilized compared to the transition state **M-TS$_2$** and **M-TS$_2$′**, respectively, (see Table 2 for relative free energy barriers), but this does not affect the regioselectivity.

In the case of the *n*-hexyl substituent, a diminished steric repulsion between ethoxy and *n*-hexyl groups changed the regioselectivity pattern. In contrast to the phenyl substituent, **M-6** in *n*-hexyl derivative had a C–N bond distance of 1.54 Å (Fig. 3a), which was 0.10 Å shorter than the corresponding phenyl derivative (Fig. 2a). This is a result of larger flexibility of *n*-hexyl chain which

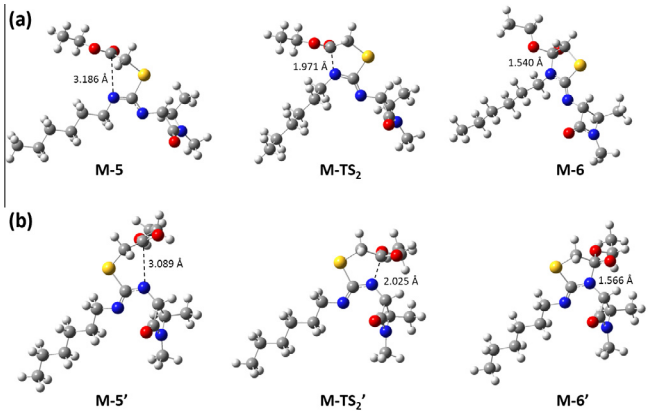


Figure 3. Optimized geometries during the five-membered ring cyclization step for *n*-hexyl derivatives of iminothiazolidinone. (a) Transformation from **M-5** to **M-6**; (b) transformation from **M-5′** to **M-6′** after conformational change of **M-5** to **M-5′**.

effectively alleviates the repulsion induced by the interaction with the ethoxy group. In the case of regioisomer **M-6′**, the C–N bond distance was 1.57 Å (Fig. 3b) which was only 0.01 Å shorter than the C–N bond distance in phenyl derivative **M-6′** (Fig. 2b). This was unsurprising since in this regioisomer the ethoxy and β-lactam groups are in interaction, as in the case of phenyl derivative. This is also reflected in the free energy barriers for this reaction (Table 2), which are very similar for all substituents. Therefore, reduced steric interactions between the *n*-hexyl and ethoxy groups are the key reason for the increased stability of **M-6** versus **M-6′** (see ESI for exact energies) which in turn results in the final product **M-7** being more stable by 1.9 kcal mol^{-1} versus **M-7′** regardless of the lower free energy barrier for the reaction of **M-5′** to **M-6′**.

Conclusions

In order to explain the different regioselectivity between aryl and cycloalkyl derivatives versus *n*-alkyl derivatives, density functional theory calculations were performed using model compounds describing the preparation of β-lactam iminothiazolidinones by the reaction of differently substituted β-lactam thioureas and ethyl-bromoacetate. Computational results were in agreement with experimental observations, showing that phenyl and cyclohexyl derivatives led to the thermodynamically more stable regioisomers which are formed by cyclization at the nitrogen atom directly attached to the β-lactam ring. In particular, they are more stable by −2.5 and −0.7 kcal mol^{-1}, respectively, than the other possible regioisomer. This occurs due to larger steric effects resulting from the repulsion between bulky substituents and ethyl bromoacetate when cyclization occurs at the nitrogen atom bearing the substituents. Conversely, in the case of *n*-hexyl derivatives the repulsion between the *n*-hexyl and ethoxy groups is lowered due to the larger conformational flexibility of the *n*-alkyl chain. This in turn results in the formation of the regioisomer with the β-lactam ring attached to the imino bond which is 1.9 kcal mol^{-1} more stable than the other regioisomer.

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Supplementary data

Supplementary data (Experimental details, calculated electronic energies, thermal corrections to free energies at 298 K, single point energies and total free energies for phenyl, cyclohexyl and *n*-hexyl derivatives **M-1**–**M-7** (Tables S1, S2, S3). References for Supplementary Data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.101.

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