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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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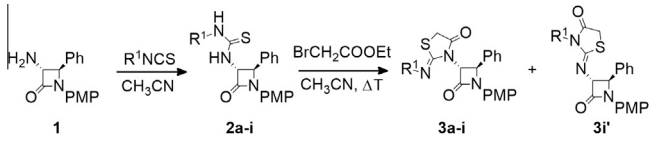
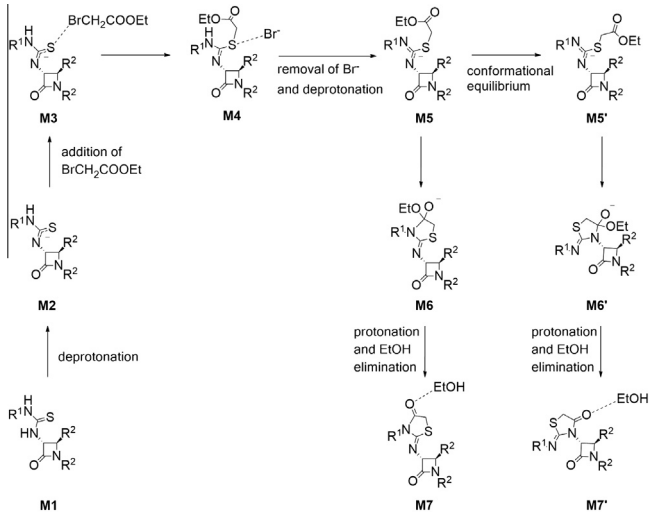


Scheme 1. Synthesis of β-lactam iminothiazolidinones **3a**–**i**/**3i′**.



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′**.

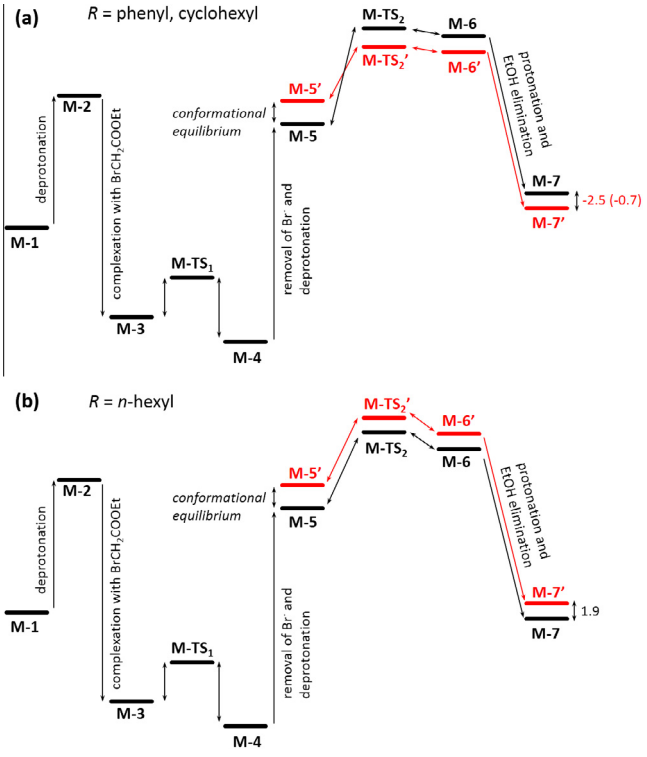


Figure 1. Schematic representation of energy diagrams in (a) phenyl, cyclohexyl and (b) *n*-hexyl derivatives of iminothiazolidinone. Free energy difference is given in kcal mol^{-1}.

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