https://doi.org/10.3311/PPch.12527

Periodica Polytechnica Chemical Engineering, 62(4), pp. 503–509, 2018

DFT Study of Stereoselective Ketene-imine Cycloadditions, Evaluation of Possible Solvent Effects with IEF-PCM

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Received: 14 May 2018, Accepted: 19 October 2018, Published online: 20 November 2018

Abstract

The formal [2+2] cycloaddition of ketenes and imines, also known as Staudinger synthesis, is a facile method for the synthesis of biologically important β-lactam derivatives. In this paper two previously reported stereoselective reactions were investigated with computational methods. Our computations support experimental data that a chiral imine, derived from D-glyceraldehyde reacting with ketenes, yields almost exclusively one out of the possible four diastereomers. The reaction proceeds stepwise, first addition of the imine to the ketene yields an intermediate, then the product is formed in a conrotatory electrocyclization. Results indicate that the electrostatic repulsion of the chiral auxiliary group is the main factor of the stereoselectivity, but solvent and substituent effects are not negligible. Calculations were performed at M06-2X/6-31+G** level of theory combined with IEF-PCM solvation, in common solvents such as toluene, THF, dichloromethane, acetonitrile and water. These results provide useful insight for the development of new chiral auxiliaries and optimizing reaction parameters.

Keywords

β-lactam, ketene, imine, cycloaddition, DFT, PCM

1 Introduction

The β-lactam antibiotics have been used in modern medicine for over 70 years, even today they are the most widely used antibacterial agents. The bicyclic β-lactam skeletons (penem, cephem, etc.) are produced by biotechnological means on industrial scale, a stereoselective total synthesis would not be cost efficient [1]. In recent years several biologically active β-lactam compounds have been discovered with different enzyme inhibition effects, these include inhibition of cholesterol absorption [2], human leukocyte elastase [3], human cytomegalovirus protease [4], prostate specific antigen [5], thrombin [6], and tryptase [7, 8]. In contrast to β-lactam antibiotics, these compounds or their precursors cannot be synthetized by microorganisms. These compounds often have stereoisomers, thus it is imperative to synthetize selectively the desired isomers. β-Lactams can also be easily transformed to other valuable compounds e.g. β-amino acids and amino alcohols. Thus, the stereoselective synthesis of the β-lactam moiety is an actively studied area [9-15]; in this paper we present a theoretical investigation on this subject.

There are several examples in the literature for the stereoselective synthesis of β-lactams; our research has been focused on the stereoselective *Staudinger* synthesis achieved by chiral auxiliaries [8, 9-23]. This reaction has been used to synthesize a wide variety of substituted β-lactam derivatives. The relative position of substituents in the 3 and 4 position of the ring are determined by the structure of the ketene and the imine [24]. The configuration of the ring can be influenced by chiral auxiliary groups or chiral catalysts. The auxiliary group can become a permanent part of the molecule or can be removed or transformed to yield the desired product.

The reaction mechanism of the *Staudinger* synthesis was studied by quantum chemical computations previously. Qi et al. investigated the reaction of cyclic imines and ketenes experimentally and also computationally concluding that reactions of cyclic imines and various ketenes yield trans lactams [25]. According to Martín-Zamora et al., in the reaction of chiral hydrazones and ketenes the selectivity is the result of the steric repulsion

Cite this article as: Komjáti, B., Szokol, B., Kováts, B., Kegye, P., Nagy, J. "DFT Study of Stereoselective Ketene-imine Cycloadditions, Evaluation of Possible Solvent Effects with IEF-PCM", Periodica Polytechnica Chemical Engineering, 62(4), pp. 503–509, 2018. https://doi.org/10.3311/PPch.12527

of the chiral auxiliary and ketene during ring closure [17]. *M*acías et al. reported the use of D-glyceraldehyde acetonide as an auxiliary; computations on a small model system gave a similar result as their experiments [16]. Lopez et al. concluded that the torquoelectronic effect, introduced by Houk, plays a relevant role in this reaction; the computations suggested that the ring closure proceeds with conrotation [26, 27]. They also found that geometries and Gibbs energies can significantly differ computed in solvent and in gas phase [28].

In this paper we present the quantum chemical modelling of two selected reactions independently published by Wagle et al. [19] and Welch et al. [20]. In both cases chiral imines, derived from D-glyceraldehyde, a convenient starting material for stereoselective synthesizes, were reacted with in situ generated ketenes yielding almost exclusively one isomer out of the possible four (see Fig. 1). The aim of our research is to determine how the chiral auxiliary controls selectivity and how solvent effects influence the reaction.

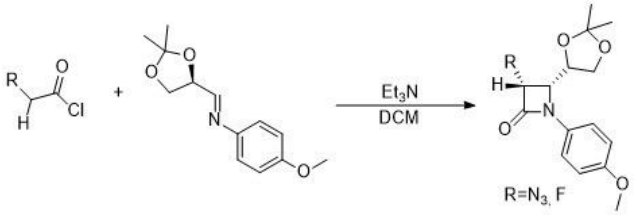

Fig. 1 Stereoselective Staudinger synthesis utilizing the D-glyceralaldehyde chiral auxiliary group, reported by Wagle and Welsch. R = N_3 and F, respectively [19, 20].

2 Computational methods

Geometries and thermochemical quantities were computed with Gaussian 09 package at M06-2X/6-31+G** level of theory, with IEF-PCM solvation model, in several solvents [29]. As opposed to previous works, a higher basis set was used and geometry optimization was also carried out in solvent [25].

Conformational analysis of all species was performed by using Avogadro [30], MMFF94 force field was applied. In each case the lowest energy conformations were used in final calculations. Vibrational analysis was carried out, starting materials, product and reaction intermediate have only positive frequencies and transition states have exactly one negative frequency. Electrostatic surface maps were made with Gabedit, figures of molecules were made with Avogadro [30, 31].

3 Results and Discussion

Previous studies on the reaction mechanisms mostly used B3LYP functional. The hybrid meta-GGA M06-2X functional, developed by the *Truhlar* group, performs consistently better than B3LYP for main group thermochemistry, due to its parameterization of mid-range dispersion is also treated well [32-36]. To choose the best functional, the structural analysis of azidoketene was performed. It was previously reported that the dihedral angle of the N-C bond is sensitive to the accuracy of computational method [37]. The dihedral angle optimized with M06-2X had only 6.9° difference, while 13.9° on average with other functionals compared to the geometry calculated with higher correlated methods e.g. MP2, MP4, and CCSD.

3.1 Reaction Mechanism

If otherwise not noted, our results for the reaction in Fig. 1. are discussed in detail wherein R is an azido group and the solvent is dichloromethane. The species in the reaction mechanism are denoted with stereodescriptors of the product they yield *e.g.* (3*R*,4*S*).

The first elementary step of the *Staudinger* synthesis is the nucleophilic attack of the imine nitrogen on the carbonyl carbon of the ketene. In the second step the electron rich enolate part of the zwitterionic intermediate attacks on the positively charged C=N double bond to close the ring [26].

The ketene can approach the imine with four different orientations, through four transition states which in general are denoted by TS1. Depending on the relative distance of the ketene's substituent (in this case the azido group) from the substituent of the imine the approaching orientation can be *exo* when the distance is larger or *endo* while it is smaller. The faces of the reacting centers within the two approaching molecules are stereoheterotopic, therefore the different approaching modes can result in different stereoisomers. Since the imine contains a chiral group, these sides are not equivalent. The possible orientations are shown in Fig. 2.

The four TS1 transition states lead to four diastereomeric reaction intermediates (INT). These structures are often represented by zwitterionic Lewis structures [28]. The relatively low barrier of the reverse reaction allows these INT structures to dissociate and to form again suggesting that these species are in thermodynamic equilibrium. The rotation barrier along the newly formed carbon-nitrogen bond is believed to be higher than the barrier of dissociation; we were unable to find the rotational

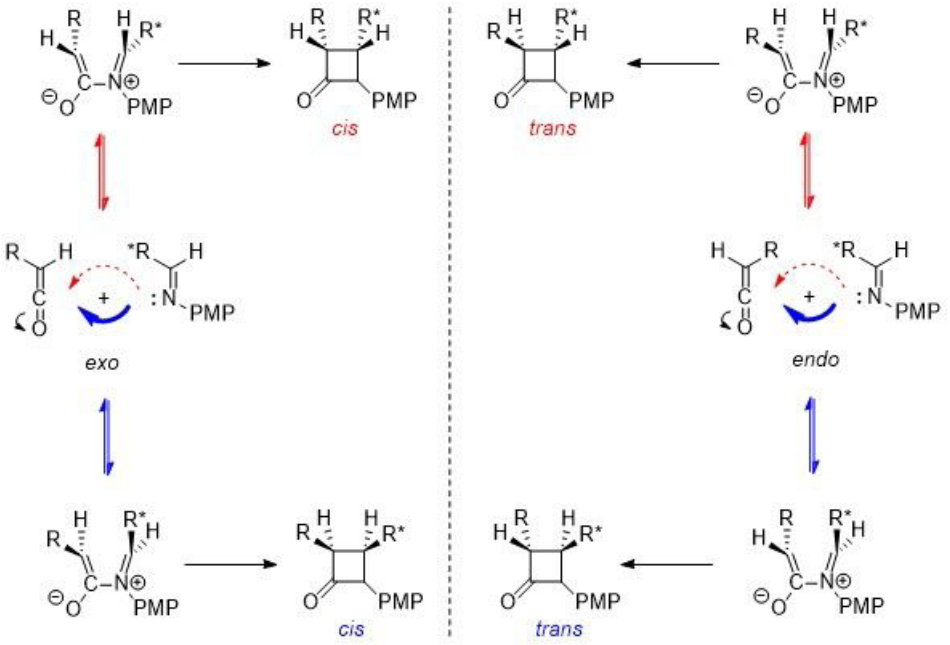

Fig. 2 Possible orientations of reacting species during Staudinger synthesis R=N_3 and F, R*= chiral auxiliary group, PMP = p-methoxyphenyl group

barrier with relaxed PES scans, because the carbon-nitrogen bond broke during rotation in every case.

The reaction intermediates (INT) complete the four-membered ring in a conrotational electrocyclization through TS2 transition states. The resulting products are stereoisomers of each other. This step is the rate limiting, the reverse reaction is only possible under extreme conditions [38]. The products cannot isomerize into each other, as postulated in the case of reaction intermediates (INT). In the reactions studied by Qi et al. [25] and Martín-Zamora et al. [17], all transition states and intermediates leading to the major product had lower Gibbs energies than those leading to minor products. We found that in our model reaction this was not the case, the formation of the *endo* intermediates have lower activation barriers than the *exo* isomers, however, in the rate limiting second step the barrier is much higher for *endo* path than for *exo* path.

Due to the higher Gibbs energies of activation for *endo* TS2's, their formation is practically negligible, only *exo* products are formed, even though *endo* intermediates have a considerably higher equilibrium population. Fig. 3 shows the Gibbs energy profile of the complete reaction, including all possible species. Fig. 4 shows the optimized geometries for species leading to the *major* product in Fig. 1, the new C-C and C-N bonds and their length are highlighted.

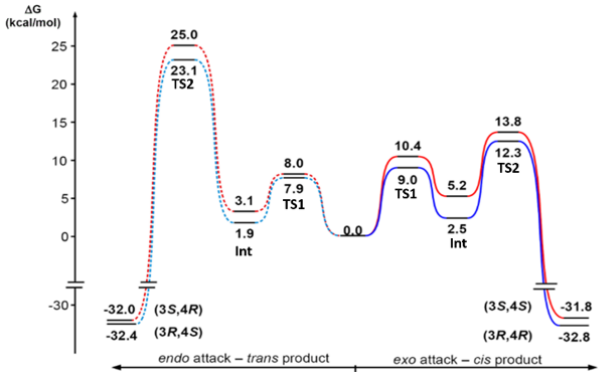

Fig. 3 Gibbs energy profile of the complete reaction pathway of azidoketene and chiral imine, including all possible isomers

3.2 Stereoselectivity

The stereoselectivity of the reaction leading to *cis* products is determined also at the second transition state (TS2). The most important difference between the (3*R*,4*R*) and (3*S*,4*S*) isomers, is the orientation of the chiral auxiliary relative to the substituent of the ketene moiety. In case of the disfavored TS2 and INT of the (3*S*,4*S*) isomer an oxygen atom of the chiral auxiliary is relatively close to the azido group or to the fluorine atom. The electrostatic potential maps in Fig. 5a and 5b show that these atoms have indeed partial negative charges, thus there is electrostatic repulsion between the chiral auxiliary and the ketene. In the favored INT and TS2 of the (3*R*,4*R*) isomer only a

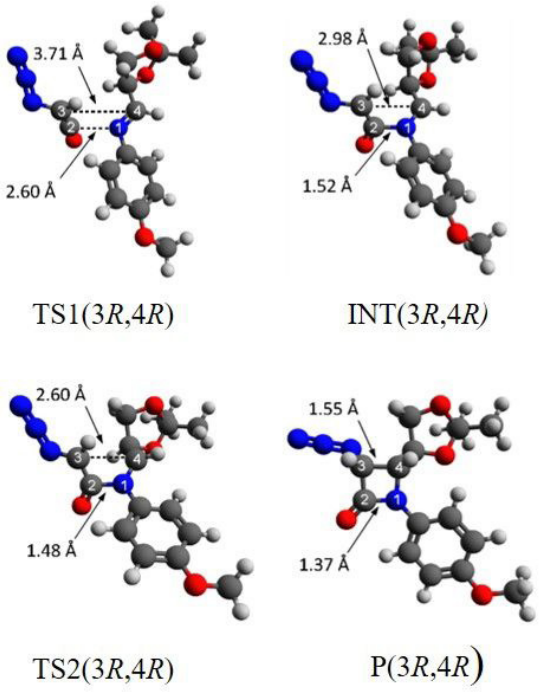

Fig. 4 Optimized geometries for species leading to the (3*R*,4*R*) major product.

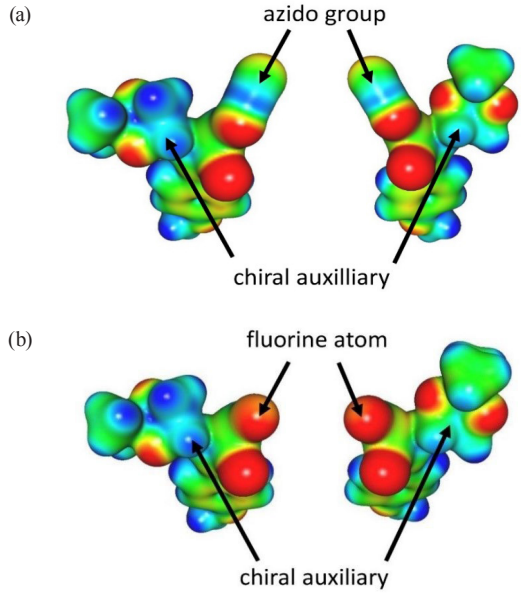

Fig. 5 (a) Electrostatic potential map of **TS2(3R,4R)** (left) and **TS2(3S,4S)** (right) for reaction of azidoketene. Red: negative charge, blue: positive charge. (b) Electrostatic potential map of **TS2(3*R*,4*R*)** (left) and **TS2(3*S*,4*S*)** (right) for reaction of fluoroketene. Red: negative charge, blue: positive charge.

moderately charged carbon and hydrogen atoms are close to the substituent of the ketene. Fluoroketene yields higher selectivity than azido ketene. This can be explained with Mulliken charges, fluorine in TS2 (3*S*,4*S*) has a charge of −0.29, the nitrogen atom in the azido group connecting to carbon atom has −0.05. These results demonstrate that not only the steric repulsion but also the electrostatic repulsion should be taken into consideration and utilized when new chiral auxiliaries are designed.

3.3 Effect of solvation

It is well known that the solvents can influence the reaction rate and even stereoselectivity of reactions [39]. Reasonable solvents for the cycloaddition reaction *e.g.* toluene, dichloromethane, tetrahydrofuran, and acetonitrile were chosen for evaluation. Water is not a suitable solvent, as it reacts with the ketene, however, to evaluate the effect of its very high permittivity (ε=78.4) it was added to the list of solvents. Unlike in previous works, geometries and thermochemical parameters were computed for each of the examined solvents.

Result of the computation using IEF-PCM solvation model should be interpreted cautiously. These calculations are not accurate enough to directly compare with experimental data. However, some trends are apparent and can be considered qualitatively correct. First, as we increased the solvent polarity from toluene to water, we observed two interesting changes. The relative Gibbs energies of almost all species dropped and the difference between the isomeric species also decreased. The decrease of activation Gibbs energies causes the increase of relative reaction rates. The free energy difference of the isomeric species is related to selectivity, the decreasing difference results lower selectivity. Results show that polar solvents stabilize the charge separation and also decrease the internal electrostatic repulsion. The dependence of stereoselectivity on the solvent also support our theory on electrostatic repulsion.

4 Conclusion

Detailed quantum chemical study of stereoselective cycloaddition of small substituted ketenes and a chiral imine derived from D-glyceraldehyde is reported at M06-2X/6-31+G**/IEF-PCM level of theory. Our computations are in good agreement with previously published experimental data, in this reaction the formation one out of the possible four isomers is favored. The stereoselectivity of the reaction is the result of the electrostatic repulsion between the chiral auxiliary group and the ketene's substituent. The effect of solvation was evaluated with IEF-PCM method in several solvents. Results indicate that the polarity of the solvent influences the reaction rate and also the stereoselectivity, but to a lesser extent. With increasing polarity the reaction

Table 1 Effect of solvation, calculated data.

		$\Delta G(INT)^a$		ΔG_{act} (TS2)^b			
	ε	(3*R*,4*R*)	(3*S*,4*S*)	(3*R*,4*R*)	(3*S*,4*S*)	de%^{c}	r.r.^{d}
Solvent				Azidoketene			
toluene	2.4	5.7	8.7	8.3	7.1	91.2	1.0
tetrahydrofuran	7.4	2.8	5.5	9.7	8.4	86.0	14.5
dichloromethane	8.9	2.5	5.2	9.8	8.6	85.3	34.5
acetonitrile	35.7	1.4	3.8	10.4	9.2	81.1	85.2
water	78.4	1.1	3.5	10.5	9.3	77.8	54.5
				Fluoroketene			
toluene	2.4	3.5	6.1	7.9	7.5	98.0	1.0
tetrahydrofuran	7.4	0.2	2.6	9.4	9.0	97.2	22.0
dichloromethane	8.9	-0.1	2.2	9.5	9.2	97.0	55.7
acetonitrile	35.7	-1.2	0.6	9.9	10.0	96.2	157.1
water	78.4	-1.4	0.3	10.0	10.0	95.8	99.3

a: Gibbs energy (kcal/mol) of intermediates relative to starting materials,
b: activation Gibbs energy (kcal/mol),
c: diastereomeric excess %,
d: relative reaction rate, based on Arrhenius equation using the same preexponential constant.

rate increases, but the selectivity deteriorates. These computational results provide useful insight for *in silico* development of new chiral auxiliaries and for optimization of reaction conditions to achieve higher yields and selectivity.

Acknowledgement

The authors are grateful for the help of Professor László Nyulászi and financial support of TÁMOP-4.2.2.B-10/1-2010-0009 grant.

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