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Mechanistic Aspects of the Ketene-Imine Cycloaddition Reactions

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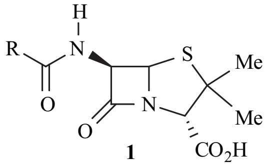
Abstract: The [2+2]-cycloaddition reaction of imines with ketenes, also known as Staudinger reaction, is one of the most commonly employed synthetic entries to the β-lactam ring. Despite this, the detailed mechanism of this reaction has remained an open debate for many years. However, the application of theoretical methods has allowed a deeper understanding of many intricacies surrounding the Staudinger reaction. The experimental evidence and the theoretical studies carried out on the Staudinger reaction mechanism, using *ab initio* and Density-functional theory methods, are reviewed. Special emphasis is placed on the competition between the concerted and stepwise reaction pathways and the origin of the stereoselectivity of the reaction.

Keywords: β-Lactams, ketene, imine, Staudinger reaction, ketene-imine cycloaddition, *ab initio* calculations.

"Dedicated to the Memory of Prof. Fernando Bernardi, Who Died Recently and Worked Very Hard for Many Years in the Theoretical Treatment of Chemical Reactivity"

I. INTRODUCTION

β-Lactams are probably the most interesting four-member rings in Organic Chemistry due to their relevance in the field of antibiotics[1]. Penicillin **1** (Fig. **1**), the first natural antibiotic to be discovered, is a bicyclic system containing a β-lactam fragment, and it is a well-known fact that its biological activity as an antibacterial is due to the presence of the β-lactam ring.

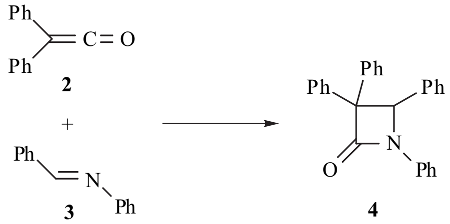


R *e.g.* =Bn, $PhCHNH_2$, $PhOCH_2$, $PhCH_2$-CO_2H

Fig. (1).

There is a variety of penicillins, bearing different groups R in the side chain [1]. Other useful antibiotics, such as cephalosporins or monobactams are also members of the family of β-lactam antibiotics.

β-Lactams were prepared for the first time by Hermann Staudinger in 1907, by reaction of diphenylketene **2** with benzaldimine **3**, leading to **4** (Scheme **1**) [2]. These compounds were considered merely a curiosity until the discovery of the chemical structure of penicillin. After the second world war, the interest in this class of compounds spurred the development of new synthetic methods allowing for the preparation of different types of β-lactam derivatives [3].



Scheme 1.

More recently, it has been reported that different types of β-lactam derivatives show new kinds of biological activities, *e.g.* as antiviral agents [4], or as inhibitors of cholesterol absorption [5].

In addition to their biological properties, the β-lactams are valuable synthetic intermediates in the preparation of β-amino acids [6], isoserine derivatives [7] or azetidines [8].

Due to the interest in β-lactam compounds, a number of synthetic methods have been developed, the most useful being cyclisation reactions [9], the addition of metallic enolates to imines [10], and [2+2] heterocycloadditions reactions. The latter group includes, in addition to the ketene-imine cycloaddition (Staudinger reaction), the reaction between isocyanates and alkenes [11], the cycloaddition between keteniminium cations and imines [12], and the Hegedus reaction between Fischer carbenes and imines [13].

The ketene-imine cycloaddtion can be carried out with a free ketene, as in the original example by Staudinger (Scheme **1**) or using an *in situ*-generated ketene. There are several methods for *in situ* preparation of ketenes [14, 15], but the most widely one employed involves acid chlorides [16].

In this review, the current situation of the mechanistic aspects associated with the [2+2]-ketene-imine cycloaddition reaction, it is examined, putting an special emphasis on the theoretical studies carried out on these kind of reactions.

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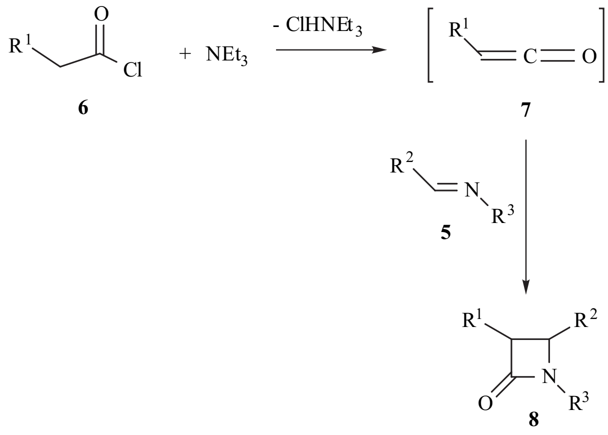
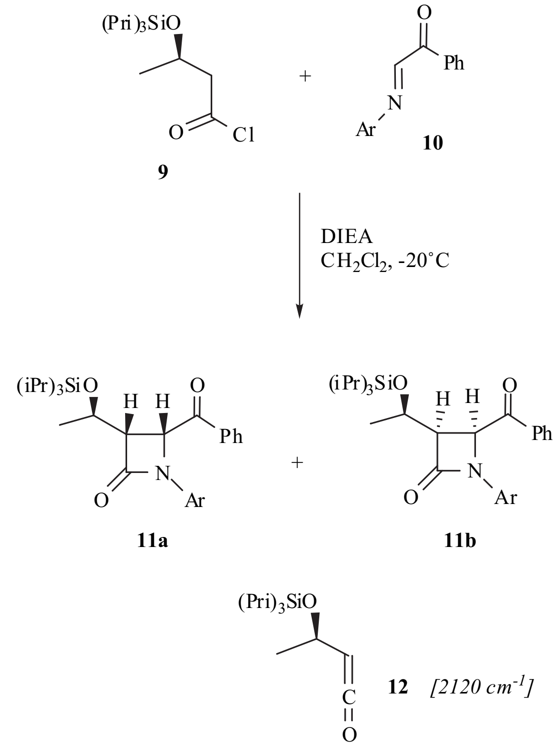
II. THE IMINE-ACID CHLORIDE ROUTE

Staudinger prepared the first stable ketene, the diphenyl ketene by dehydrohalogenation of the 1,1-diphenyl acetyl chloride, using triethylamine as a base. However, ketenes are generally quite unstable compounds [14], undergoing dimerization or hydrolysis, and usually they are not isolated, but prepared and used *in situ*. This procedure (Scheme **2**) is generally known as the imine-acid chloride route. Imine partner **5** and triethylamine are added to a solution of the corresponding acid chloride **6**, which originates the ketene **7**. The [2+2]-cycloaddition of **7** with **5** leads to β-lactam **8**.

It is assumed that, as the ketene forms, due to the action of the base on the acid chloride, it reacts with the imine. However, part of the controversy surrounding the mechanism of the ketene-imine cycloaddition reaction is due to the fact that usually not a "true ketene" but an acid chloride is actually mixed with the imine as a reactant.



Scheme 2.



Scheme 3.

This point has been addressed by Lynch and co-workers by means of low-temperature FT-IR spectroscopy [17]. These authors studied the reaction of acid chloride **9** (see Scheme **3**) with imine **10**, in the presence of diisopropylethylamine (DIEA), to give diastereoisomeric β-lactam derivatives **11a** and **11b**.

The formation of the ketene **12** was confirmed by the observation of a strong band at 2120 cm^{-1}. According to kinetic studies, β-lactam derivatives **11** arise completely from the ketene intermediate.

In addition, the reaction leading to the formation of ketenes by dehydrohalogenation of acyl chlorides has been studied theoretically, using density-functional theory [18].

These studies allowed the transition structures corresponding to the dehydrohalogenation step of acetyl chloride and methoxyacetyl chloride to be located at the B3LYP/6-31G* level of theory. As can be seen in Fig. **2**, (transition structures **13** and **14**), trimethylamine acts as a base, deprotonating the α carbon atom of the acyl chloride. At the transition structures, the carbon-hydrogen and the carbonyl-chlorine bonds are completely broken. The predicted values of the activation barriers are 23.4 and 26.1 kcal mol^{-1}, respectively.

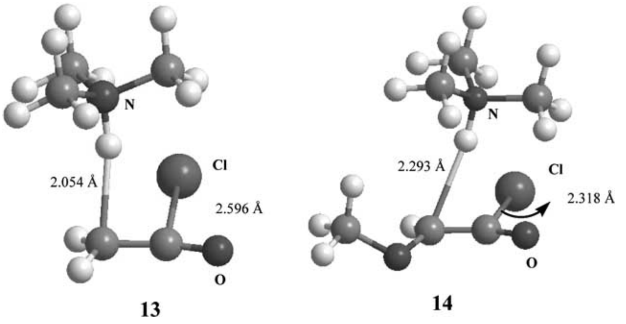
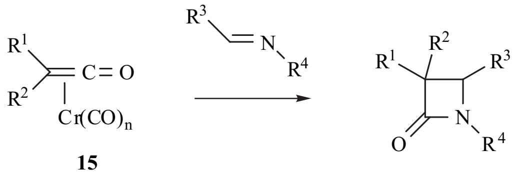


Fig. (2).

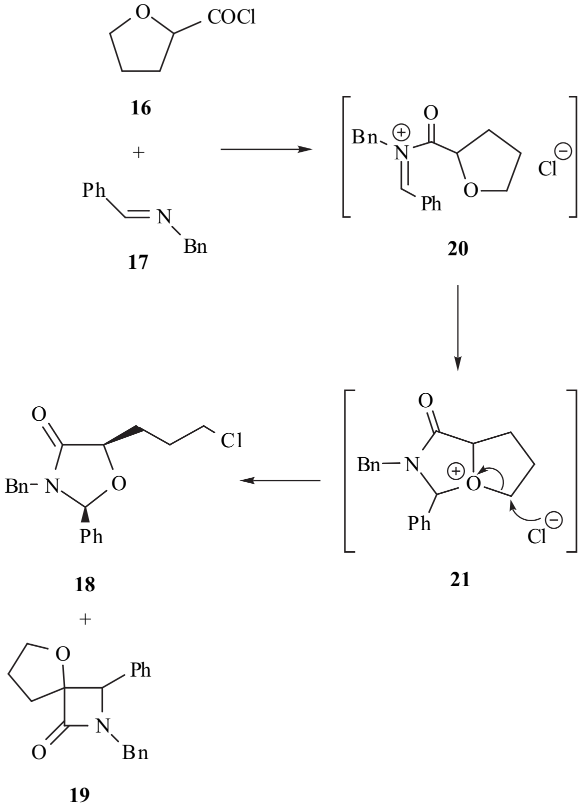
In addition to the previous results, it is noteworthy that in the Hegedus reaction the participation of a chromium-coordinated ketene (**15**, Scheme **4**) has been proposed, which will experience the nucleophilic attack of the imine to give the corresponding β-lactam [19].



Scheme 4.

Inspite of the evidence about the participation of ketenes on the imine-acid chloride reaction it has been also shown that the mixture imine-acid chloride can undergo side reactions not involving the formation of a ketene. Thus, in the reaction of 2-tetrahydrofuroyl chloride **16** (Scheme **5**) with *N*-benzylbenzaldimine **17** the formation of side-product **18** in addition to β-lactam **19** was observed. The formation of **18** can be explained by assuming the initial acylation of **17** to give the *N*-acyliminium intermediate **20**. The internal nucleophilic attack of the oxygen on the iminium carbon atom leads to the bicyclic intermediate **21**, which in turn undergoes the ring opening by chloride ion [20]. Also, the formation of acyliminium intermediates in the imine-acid chloride reaction has been studied by NMR [21].

Despite the existence of side reactions, it can be concluded that free ketenes are formed in the acid chloride reaction.

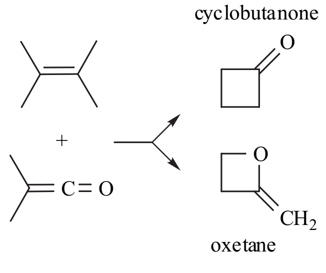


Scheme 5.

The formation of a β-lactam in the acid chloride reaction involves a formal [2+2]-cycloaddition reaction as in the case of the original reaction discovered by Staudinger (Scheme **1**). Of course, also a formal [2+2]-cycloaddition has been invoked in the cases of reactions in which the ketene is generated by a different method, as happens in the Hegedus reaction [19] or in the case of the reaction of cyanoketenes [15].

III. [2+2]-CYCLOADDITION REACTIONS OF KETENES

The cycloaddition between cumulenes and olefins is normally used to obtain cyclic compounds otherwise difficult to prepare. The large amount of experimental work performed on this reaction has shown that heterocumulene $R_2C{=}C{=}O$ in general prefers to react, in cycloadditions with olefins, with the C-C double bond rather than the carbonyl group yielding cyclobutanones instead of oxetanes (Scheme **6**).



Scheme 6.

In principle stereochemical and kinetic evidence supports a [2s + 2a] concerted mechanism between a suprafacial olefinic reactant and an antarafacial ketene in agreement with the Woodward–Hoffman rules. However, more recent developments over the Woodward–Hoffmann rules [22] and theoretical results on cycloadditions between olefins, have suggested not overlooking other mechanisms [23]. These mechanisms are concerted, two-stage and two-steps pathways involving diradical or zwitterionic species. In fact, according to Epiotis [22], the WH rules can be modified depending on the nature of reactants. Non-polar cycloadditions should occur *via* a two–step mechanism, whereas, polar [2+2] cycloadditions should occur *via* a concerted approach. Bernardi *et al.* addressed this point and, using CAS-SCF methods [22h], studied and compared the case of a few prototypical polar and non polar [2+2] cycloadditions. For all the systems they were able to detect a two-step biradical mechanism, but only for the polar systems the occurrence of a concerted transition state. The two-step biradical mechanism is not influenced by the presence of polar substituents or heteroatoms, and the effective pericyclic transition state remains very high in energy being not energetically competitive with the two-step mechanism. The idea, suggested at the end of the study, was that in the presence of a polar solvent, the concerted approach could become important. On the other hand, in a later study of the reaction of dicyanoethylene and hydroxyethylene, investigated including the solvent effect *via* continuum models, it was shown that the solvent can also strongly stabilize the intermediate occurring in the two-step mechanism, leaving the concerted approach high in energy [22i].

In the early nineties, a few important theoretical studies were published helping to shed light on the mechanism.

In one of the first papers, Bernardi *et al.* examined the existence of supra–antara transition states [24], by studying, at MC-SCF level with STO-3G and 4-31G* basis sets, the [2s+2a] approach of three parent reactions, the cycloaddition reaction of ethylene, with, respectively, ethylene, singlet O_2 and ketene. In their study they discovered that the symmetric saddle points corresponding to the supra–antara approach (Fig. **3**) are not true transition structures but rather a local maximum with two directions of negative curvature. In other words, they established that, in these three cases and at this computational level, the supra-antara symmetric reaction pathway does not exist. Afterwards, the work was extended to a more detailed study on the Potential Energy Surfaces of the [2 + 2] cycloadditions of ketenes.

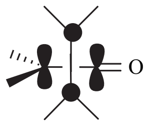
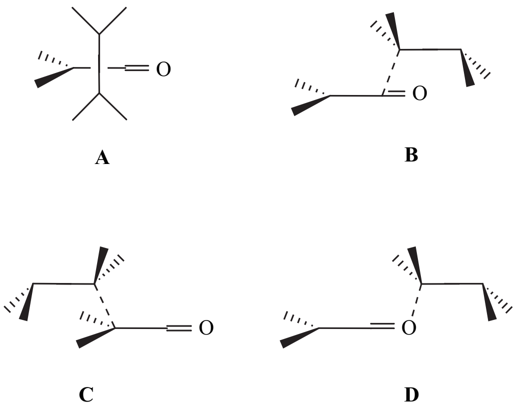


Fig. (3).

Houk *et al.* [25] carried out MP2 calculations at 6-31G* basis set level to study the reaction of ethylene and propene with ketene and methylketene.

At this computational level they found, for every reaction, only one transition state attributing to a concerted attack of [2+2+2] type where the LUMO of the carbonyl group interacts with the HOMO of the alkenes. This structure has an almost fully-formed bond between the central carbon of the ketene and one carbon of the ethylene and the other incipient bond much longer. As a consequence this transition state has a carbenoid character showing a strong similarity with those of hydroborations and of carbene cycloadditions to alkenes [26]. The central carbon of the ketene is, at the same time, electron donor with the $\pi_{C=C}$ orbital and acceptor with the $\pi_{C=O^*}$ orbital.

In a subsequent paper, Bernardi explored both, in the parent reaction, ketene + ethylene, the possibility of a concerted supra-antara approach and the possibility of non-concerted reaction paths involving diradical species (see Scheme **7**). For this reason these authors used MC-SCF theory where zwitterionic and biradical mechanisms can be treated in a more balanced way in the description of the topology of the Potential Energy Surface [27].



Scheme 7.

The more energetically favored mechanism (**B**) was a highly asynchronous process involving the formation of a short-lived diradical intermediate with a gauche conformation involving the central carbon of the ketene (see Fig. **4**). This result is in agreement with the concerted nature of this reaction.

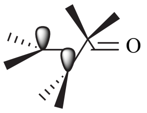
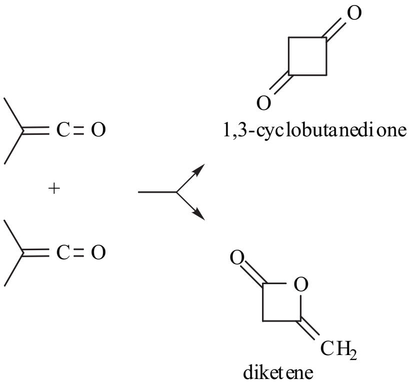


Fig. (4).

The same authors, when analyzing and rationalizing the Potential Energy Surface, using the valence bond (VB) model, inferred that in the case of formation of the cyclobutanone the topology of the PES was virtually identical to the case of ethylene dimerization [28].

Seidl and Schaefer [29] studied the dimerization of the ketene. This reaction can yield two different products, diketene and 1,3 –cyclobutanedione (Scheme **8**).

The work was addressed to describe the two different mechanisms and to test the existence of the [2s +2a] pathway. In fact, the dimerization of ketene represents the more symmetric and less hindered case of possible supra–antara reaction. Unlike Bernardi *et al.,* who used MCSCF methods with a small basis set, they put emphasis on the correlation to provide an accurate treatment of the energy of the reaction using a large basis set and CISD+Q and CCSD theory level to correct the energy. Their results showed that the formation of the diketene, consistent with a [2+2+2] type of mechanism, was favored in comparison with the formation of 1,3-cyclobutanedione, but the height of the barriers were comparable and substituents on ketene could change the mechanism of the reaction, thus stabilizing the formation of cyclobutadienones. Moreover, a symmetric supra–antara approach does not exist.



Scheme 8.

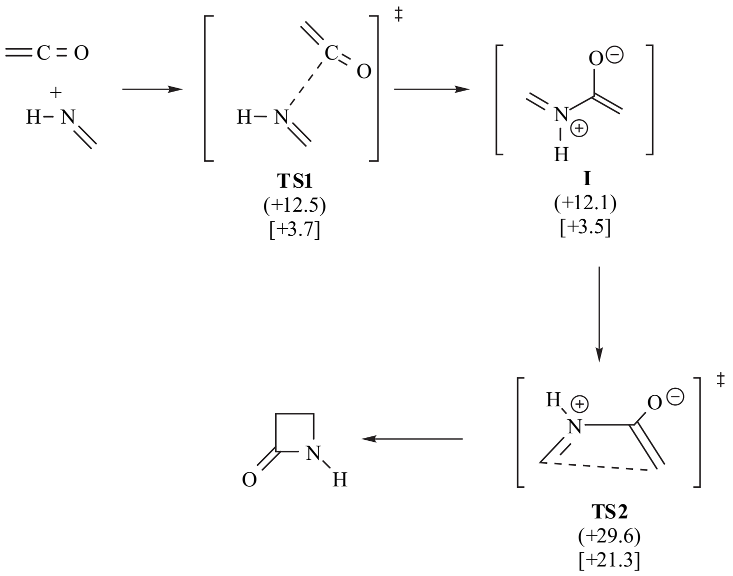
To sum up the results, the multi-configurational approach with small basis sets provides a description comparable with the topological characteristics of the ethylene + ethylene involving biradical structures, whereas the SCF higher basis sets with correlation energy are inclined to a [2+2+2] type of approach.

In spite of these differences, the results are in good agreement with the experimental outcome and "conceptually consistent": [28] the supra–antara approach does not exist, all the reactions are non-synchronous and concerted with the central carbon of ketenes involved in the first forming bond.

IV. *AB INITIO* STUDIES ON THE MODEL STAUDINGER REACTIONS

Despite its interest, the [2+2]-cycloaddition of ketenes with imines was not a subject of theoretical research using *ab initio* methods, until 1992. In a communication, Sordo and co-workers reported the results of the *ab initio* calculations at the HF/6-31G* and MP2/6-31G* levels of theory on the reaction of ketene with formaldimine (Scheme **9**) [30].

At the levels of theory considered two saddle points and a minimum (in addition to reactants and product) were located. The first saddle point **TS1** corresponds to the transition structure for the nucleophilic addition of the imine nitrogen to the central carbon atom of the ketene. After the first transition structure, zwitterionic intermediate **I** is formed. Transition structure **TS2** corresponds to the conrotatory ring closure of the intermediate, thus giving β-lactam. The computed relative energies are shown in Scheme **9**.



Scheme 9. The energies are in kcal mol^{-1}. The results between parenthesis were obtained at HF/6-31G* level of theory and those in brackets correspond to the MP2/6-31G* level of theory.

The formation of a zwiterionic intermediate is consistent with the experimental results obtained previously [15, 17, 31].

As can be seen, the ring closure of the intermediate is the rate-determining step of the process. In this context, it is interesting to note the close similarity between **TS2** and the transition structures of the electrocyclic ring opening of cyclobutenes located by Houk and co-workers [32].

The formation of a zwitterionic intermediate suggests that the Staudinger reaction could be strongly influenced by the solvent polarity. Thus, at the MP2/6-31G* level of theory, if the zero-point energy correction is taken into account, the zwitterionic intermediate is no longer a stationary point of the potential energy surface, thus making the reaction a one-step process. However, it is to be expected that structures showing a certain level of charge separation will be stabilized, as the solvent polarity increases. In fact, the Staudinger reaction is usually carried out in moderately polar solvents, e.g. CH_2Cl_2.

In order to establish the importance of the solvent effects on the reaction mechanism, *ab initio* calculations were carried out using a continuum model to take into account the solute-solvent electrostatic interaction [33].

The increased solvent polarity, causes an earlier **TS1**, with smaller charge transfer and an important stabilization of zwitterionic intermediate **I** and **TS2**, with no significant changes in the geometry (see data in Table **I**).

According to the previous results, it was established that the ketene-imine cycloaddition reaction presents a two-step mechanism.

A more complete study of the parent reaction between formaldimine and ketene has been carried out recently at the MCSCF level of theory [34].

The stationary points were optimized at the CASSCF/aug-cc-pVDZ level of theory, using an active space of 8 electrons and 7 orbitals (π and π* orbitals of the imine and ketene and the n_σ lone pair of the nitrogen).

Table I. Solvent Effects on the Staudinger Reaction[a]

	Theory Level	Reactants	TS1	I	TS2
Vacuum	HF/6-31G*	0.0	12.5	12.1	39.6
	ZPE (6-31G*)	48.6	51.8	52.8	52.2
	MP2/6-31G*	0.0	3.7	3.5	21.3
Solvent					
ε = 2.21	HF/6-31G*	0.0	10.3	7.6	36.3
	ZPE (6-31G*)	48.6	51.5	53.1	52.3
ε = 37.5	HF/6-31G*	0.0	8.5	1.3	31.4
	ZPE (6-31G*)	48.5	51.0	53.3	52.3

[a] Relative energies (to reactants) in kcal mol^{-1}.

Two shallow intermediates, having *trans* and *gauche* conformations, **M *Trans*** and **M *Gauche***, connected to the reactants through the corresponding transition structures, and two electrostatic minima, were located. **M *Trans*** has a planar transoid butadiene-like structure, while **M *Gauche*** can be considered a flat zone of the surface.

The **M *Gauche*** intermediate is connected to the final product, β-lactam, through transition structure **TS1**, which shows the two terminal methylene groups with conrotatory rotation. There are significant differences with the previous mechanisms:

a) two approaching pathways of the reactants are located, the *gauche* transition structure being higher in energy by 4.7 kcal mol^{-1}.

b) the *trans* pathway is not an active reaction channel, because it was not possible to find on the potential energy surface a pathway connecting the **M *Trans*** with the product or with the **M *Gauche*** intermediate.

Despite the fact that the *trans* pathway is not active in the gas phase, we must note that the presence of a polar solvent should stabilize the zwitterionic intermediate region more than the transition state zone, thus making the trans pathway active because **M *Gauche*** and **M *Trans*** will be connected by a conformational transition state.

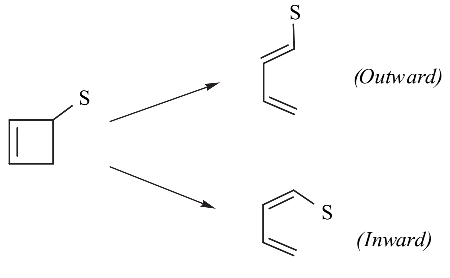
The mechanism of the related reactions of ketenes with *N*-silylimines has also been studied experimentally and theoretically, using *ab initio* [35] and density-functional methods [36]. According to these studies, the reaction proceeds in two steps, the first being the addition of the imine to the ketene and the transfer of the silicon moiety to the oxygen giving a 2-azadiene system which than undergoes the conrotatory cyclization to the β-lactam.

V. STEREOELECTRONIC EFFECTS ON THE STAUDINGER REACTIONS

As stated before, the mechanism of the Staudinger reaction (at least when being carried out in solution as is the usual case, in moderately polar solvents) involves the conrotatory ring closure of a zwitterionic intermediate in close analogy with the ring opening/ring closure of 2-cyclobutenes. In this context, it is possible to think, that the torquoelectronic effect [37] could eventually play some role in the stereoselectivity of the reaction. For example, in the case of synthesis of 3-fluoro-azetidinones by Araki and co-workers [38], the observed selectivity was probably not related to pure steric effects, as the selectivity was retained even when more bulky ketenes were employed in the reaction.

A possible explanation for the stereoselectivity in this and other Staudinger reactions can be derived from the participation of the torquoelectronic effect in the second step of the reaction, namely, the conrotatory ring closure of the zwitterionic intermediate. Thus, in the case of the ring opening of 3-substituted cyclobutenes (see Scheme **10**), two possible products are possible, depending on the position of the substituent.

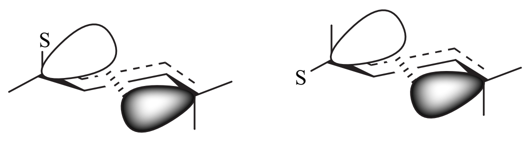
The explanation for this effect, developed by Houk and co-workers [37], lies in the interaction between group S and the σ breaking-bond in the ring-opening transition structure.



Scheme 10.

If the S group is a donor one, the interaction in the inward position will be destabilizing (see Fig. **5**) and the outward product will form preferentially.

However, if S is an acceptor, the interaction with the σ breaking-bond will be favourable, and the inward product will form.



Transition state *inward* Transition state *outward*

Fig. (5).

In the case of the ketene-imine cycloaddition, this effect was investigated and detected by an *ab initio* study. The transition structures corresponding to the ring closure of the zwitterionic intermediate in a series of Staudinger reactions were located at the HF/6-31G* level of theory. In this model of calculations, donor and acceptor groups were considered, and the difference in energy for the inward and outward closure was evaluated (see Table **II**).

As can be seen in Table **II**, the donor groups, such as hydroxyl, or halogens, exhibit a strong preference for the outward rotation, while a strong acceptor, such as BH_2, prefers to rotate inward in the transition structure. The torquoelectronic effect on the Staudinger reaction was also shown to be influenced by the solvent polarity [39].

According to precedent studies, it is important to take into account that the stereoselectivity of the Staudinger reactions is a complex issue, in which several factors, in addition to the steric effects, can play a significant role.

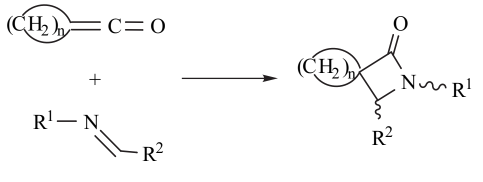
Table II. Torquoelectronic Effect on the Staudinger Reaction^a

S	E (inw-outw) (HF/6-31G)	E (inw-outw) (MP2/6-31G*//6-31G*)
OH	10.1	12.3
Cl	9.8	12.7
F	9.6	11.2
CH_3	8.8	8.5
H	0.0	0.0
BH_2	-12.6	-14.9

^{a}Energies in kcal mol^{-1}.

VI. STAUDINGER REACTIONS OF CYCLIC KETENES

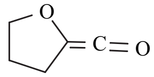
In recent times, our group has developed an intensive study about the stereoselectivity of the [2+2]-cycloaddition reactions of cyclic ketenes with imines (see Scheme **11**) [40, 41]. In these reactions, the two substituents of the ketene form part of a ring, so a spiro-β-lactam is formed in the reaction (see Scheme **11**).



Scheme 11.

In all the cases studied, a heteroatom was present in the ketene ring. This allowed the relative weight of the steric and torquoelectronic effects on the reaction stereoselectivity to be determined.

The corresponding model reactions (see Scheme **12**) were studied at MP2/6-31+G* or Becke3LYP/6-31G* levels of theory.



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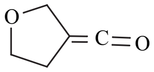

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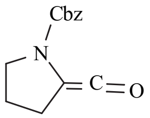
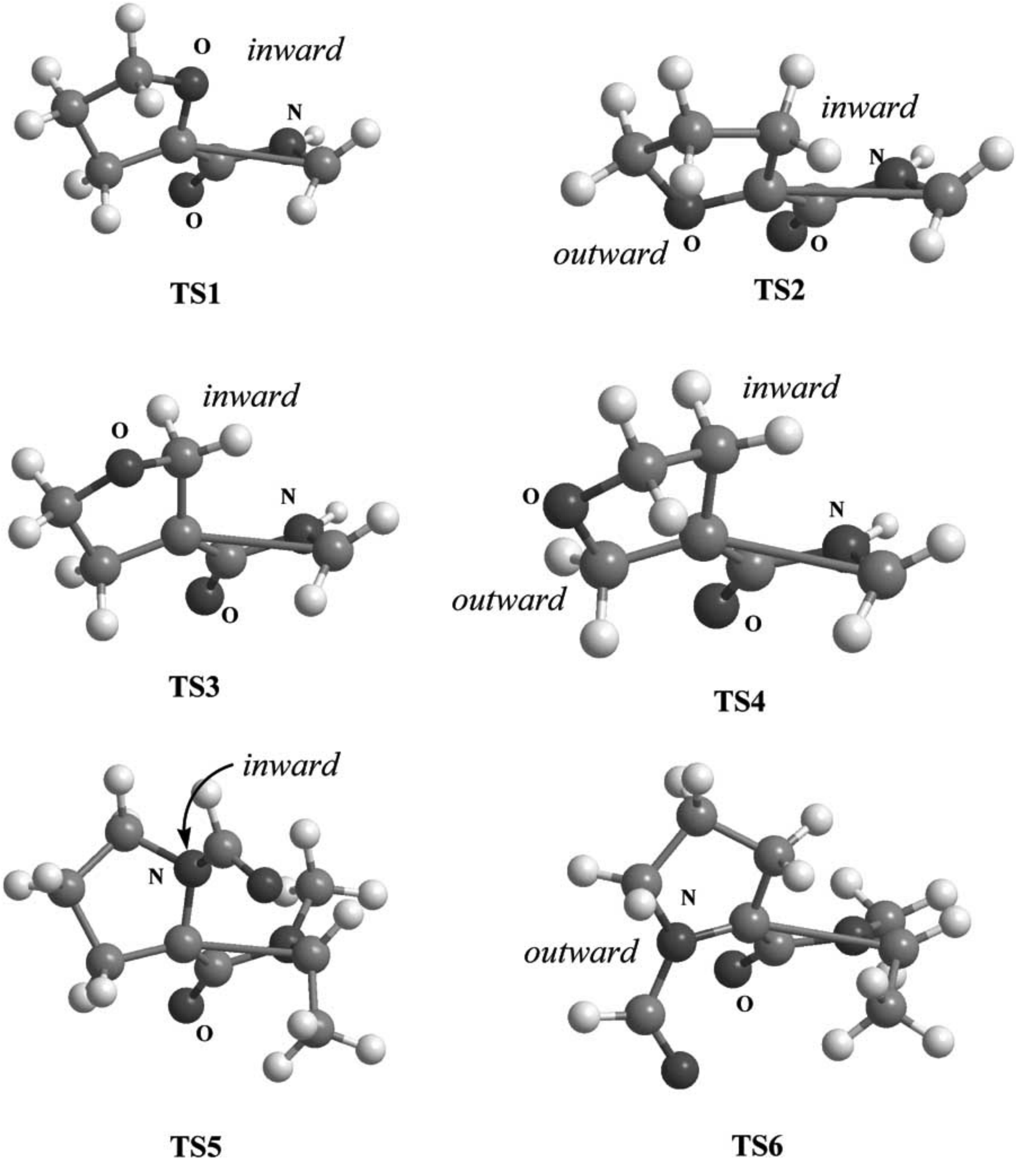


26

Fig. (6).

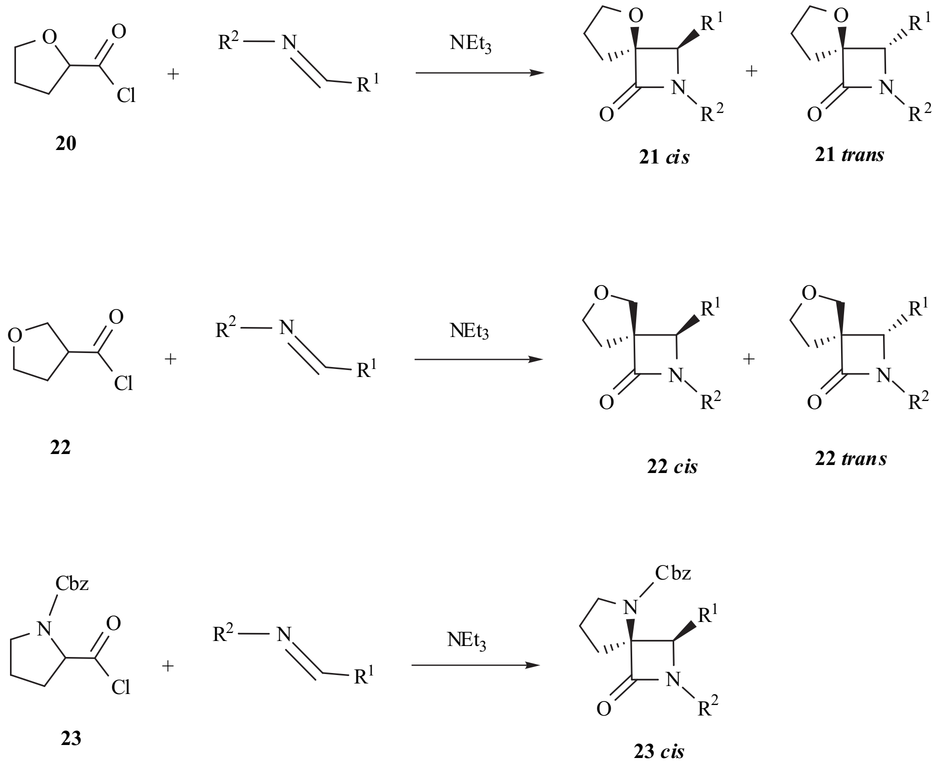


TS1 **TS2**

TS3 **TS4**

TS5 **TS6**

Fig. (7).



Cbz = benzyloxycarbonyl

Scheme 12.

The theoretical study was carried out assuming that in all cases, the “acid chloride route” was to be followed, leading to the formation of the corresponding ketenes **24-26** (see Fig. **6**), as was discussed in part II of the review.

According to the MP2/6-31+G* calculations on the reaction of ketenes **24**, and **26**, in the transition structure corresponding to the conrotatory ring closure, there is a strong energetic preference for the heteroatom to occupy the outward position (see Fig. **7**).

In the case of the reaction of ketene **24**, transition structure **TS2** is 2.1 kcal mol^{-1} more stable than **TS1**, which has the oxygen in position inward. The steric effects are almost negligible in this case, and will contribute to stabilize **TS1** and not **TS2**.

This behaviour is consistent with the previous discussions and the data shown in Table **II**. The experiments carried out support this statement; thus in Table **III**, some results are indicated regarding the stereoselectivity of several of the reactions shown in Scheme **12**. As can be seen (entries 1-4) the stereoselectivities observed are quite important. The case of entry 5 seems to point to a possible change in the mechanism of the cycloaddition reaction.

On the other hand, in the case of the ketene **25**, there is almost no effect, because the electronic nature of the two methylene groups placed in the inward and outward position is the same. Thus, the energetic difference between **TS3** and **TS4** is only of 0.2 kcal mol^{-1}, and, consequently, the stereoselectivity is quite low (see Table **III**, entries 6-8).

The effect of the nitrogen is more pronounced. According to the calculations the preference for the outward rotation is of 8.7 kcal mol^{-1} (**TS6** is clearly favoured). As can be seen in Table **III** (entries 9-11) only one stereoisomer is formed in this reaction.

The torquoelectronic effect appears to influence also some related reactions, according to the experiments by Hegedus and co-workers [19].

Table III. Stereoselectivity of Some the Staudinger Reactions Outlined in Scheme 12

Entry (ketene)	R^1	R^2	*Cis*:*Trans* ratio
1 (**24**)	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	15:1
2 (**24**)	C_6H_5	p-$CH_3OC_6H_4$	12:1
3 (**24**)	C_6H_5	CH_3	14:1
4 (**24**)	2-Furyl	p-$CH_3OC_6H_4$	8:1
5 (**24**)	p-$NO_2C_6H_4$	p-$NO_2C_6H_4$	1:5
6 (**25**)	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	3:1
7 (**25**)	C_6H_5	p-$CH_3OC_6H_4$	3:1
8 (**25**)	p-$NO_2C_6H_4$	C_6H_5	1:2
9 (**26**)	C_6H_5	CH_3	Only *cis*
10 (**26**)	C_6H_5	p-$CH_3OC_6H_4$	Only *cis*
11 (**26**)	C_6H_5CH=CH-	p-$CH_3OC_6H_4$	Only *cis*

CONCLUSIONS

The Staudinger reaction, a valuable tool in organic synthesis can be considered in general as a polar, stepwise reaction, in which the ketenes and the imines react to form a zwitterionic intermediate, strongly stabilized by polar solvents.

According to the *ab initio* studies carried out, the conrotatory ring closure of this intermediate lead to the β-lactam product.

The stereoselectivity of the reaction appears to be the result of a combination of steric and electronic effects. In some examples, the role played by the torquoelectronic effect has been demonstrated by experimental and theoretical methods.

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