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A CASPT2 and CASSCF Approach to the Cycloaddition of Ketene and Imine: A New Mechanistic Scheme of the Staudinger Reaction

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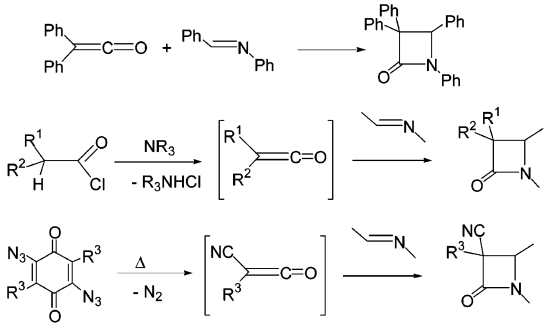
Abstract: We report a new theoretical study of the mechanism of the parent Staudinger reaction between ketene and formaldimine. This mechanism, in contrast with previously reported computational studies, involves the formation of two different intermediates, *gauche* and *trans*, which can be interconnected on the potential energy surface depending upon reaction conditions. This novel CASPT2/CASSCF mechanistic scheme may be considered a new starting point to rationalize stereochemical outcome and solvent effects in these reactions.

The Staudinger reaction and its variants are one of the most efficient synthetic methods for the preparation of β-lactams. The β-lactam ring is present in antibiotics such as penicillins and cephalosporins and is the precursor of other compounds of biological importance such as the β-amino acids.[1] In 1907, Staudinger discovered that a β-lactam is formed from the reaction of diphenylketene with benzylideneaniline,[2] and a number of ketenes and imines have been shown to undergo this type of [2 + 2] cycloaddition reaction.[3a] Several variants of this reaction (see Scheme 1), in which the ketene is formed in situ from precursors such as acyl chlorides or diazido-1,4-benzoquinones, have been described.[4]

A critical feature of the Staudinger reaction is the control of the relative and absolute stereochemistry of the two chiral centers of the β-lactam formed.[3b] This target, despite numerous attempts, remains a difficult synthetic goal and has directed researchers toward the investigation of the mechanism at a theoretical level. On the other hand, the amount of variables affecting this polar cycloaddition, which is strongly influenced by the solvent, also renders difficult the theoretical approach.

SCHEME 1



In general, theoreticians have challenged the problem by inserting solvent effects in the calculation, trying to keep the computational level within reasonable limits. This point has led to theoretical studies where HF, DFT and MP2 methods have been combined, thereby limiting the investigation of the role of the solvent to applications of a simple dielectric continuum self-consistent reaction field (SCRF) model.[5] Only recently Truong has examined the possibility of a more accurate incorporation of the solvent effects using the GCOSMO dielectric continuum solvation approach.[6] Despite substantial agreement with experimental results in detecting the solvent effect to transform a single-step process for the gas-phase model into a two-step process where the solvent stabilizes a zwitterionic intermediate, some perplexities derive from the description of the potential energy surface (PES), suggesting that a further investigation at the theoretical level is necessary. Some of the theoretical descriptions of the mechanism of the reaction are in contrast with each other, and at present, an asynchronous concerted reaction pathway, a nonconcerted mechanism with different possible intermediates (diradical, zwitterionic, or both), or simply a more detailed mechanistic scheme cannot be excluded.[7] Moreover, according to previous theoretical studies, the only important prediction about the stereochemistry of the products is related to the torquoelectronic effect, which may be only in part responsible for the different stereoisomers that are normally obtained from the Staudinger reaction.[8,3b] In our opinion, a good opportunity for removing all doubts about a correct description of the PES is to study the reaction mechanism using CASSCF methods. It is well-known, in fact, that this level of theory is more suitable for treating the various electronic species involved in a reaction mechanism in a balanced way.[9]

In this paper we present the results obtained in the study of the potential energy surface for the parent cycloaddition reaction between ketene and formaldimine (see Scheme 2), at the MCSCF computational level.

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(1) For a detailed description of the preparation and synthetic utility of β-lactams, see: *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1993.

(2) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51.

(3) (a) A comprehensive description of the chemistry of ketenes can be found in: *Ketenes*; Tidwell, T. T., Ed.; Wiley: New York, 1995. (b) For a recent review on asymmetric Staudinger reaction, see: Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, *3223*, 3.

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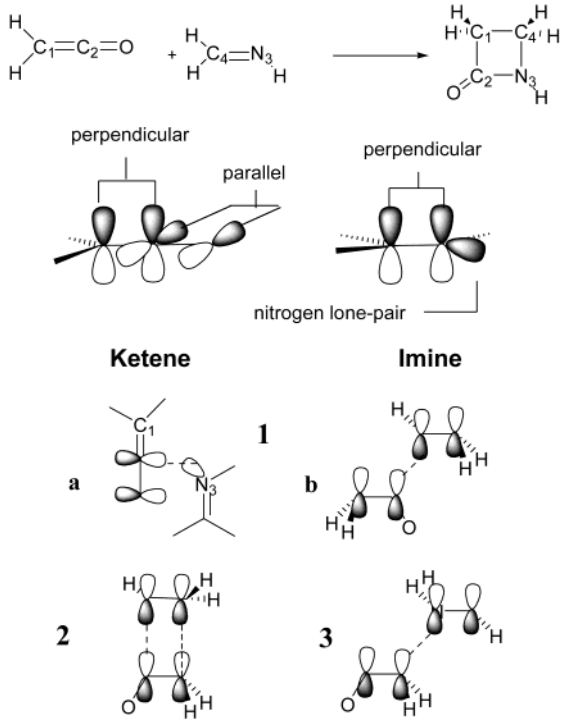
SCHEME 2



Scheme 2, where the more reasonable alternative pathways have been divided depending on the starting bond formation and the orbitals involved, shows that the formation of β-lactams, through this reaction, has a very extensive PES, the entire study of which is beyond the scope of this work. In pathway **1** the first forming bond is N_3-C_2 where the **1a** pathway involves the lone pair of the imine and the parallel π system of the ketene whereas the **1b** pathway involves the two perpendicular π systems. Pathway **2** takes into account the concerted formation of N_3-C_2 and C_1-C_4 bonds using the two perpendicular π systems. The **3** pathway takes into account the initial formation of the C_1-C_4 bond using the two perpendicular π systems.

The aim of the paper is to investigate the pathway **1a**, which is the most widely accepted mechanism corresponding to the low energy nucleophilic addition of the imine to the more electrophilic carbon of the ketene to give a zwitterionic intermediate before the electrocyclic closure to the products. The study has the scope, besides being a detailed description of the mechanism, of detecting an energy barrier to compare with the other possible mechanisms whose preliminary results will be here discussed.

Our results change the mechanistic reference scheme of the reaction and lead to new investigations of the solvent and substituent effects on the mechanism of the reaction. Despite the difficulties in describing the mechanism using a gas-phase computational model, our study supports the idea of a more complex potential energy surface involving the possibility of two different molecular approaches (*gauche* and *trans*), their interconnection depending upon the reaction conditions. The relevance of our theoretical results to the stereochemical outcome of the reaction is also discussed.

The most relevant geometrical parameters of the stationary points found for the *gauche* and *trans* approach and the energy profiles for these reaction pathways are shown in Figures 1 and 2, respectively.

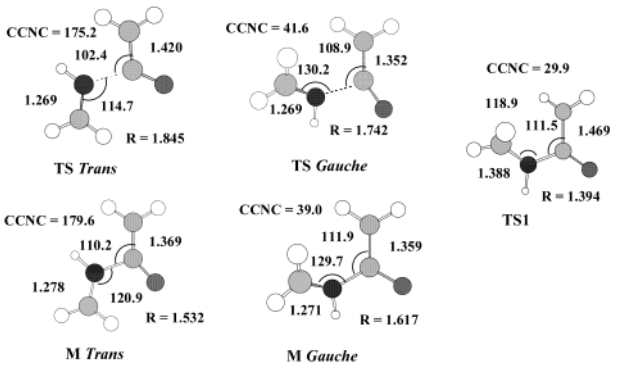


FIGURE 1. Relevant geometrical parameters for the fully optimized structures at CASSCF/aug-cc-pVDZ level (bond lengths in Å and angles in deg). *R* is the C−N forming bond, and CCNC is the CC(ketene)−NC(imine) dihedral angle.

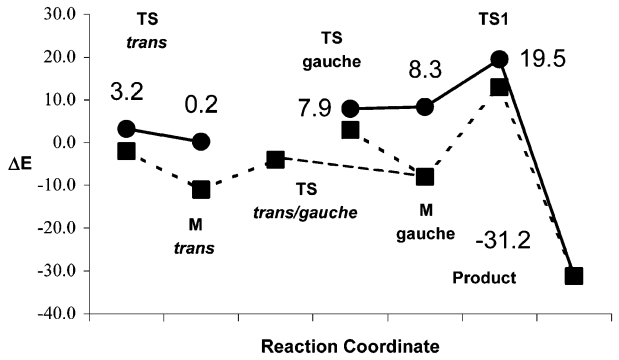


FIGURE 2. Energy profile of the parent ketene + imine reaction (solid line, ●) showing that there is no connection between M *trans* and M *gauche* intermediates. The relative energies (kcal/mol) correspond to the CASPT2/aug-cc-pVDZ + ZPE values. The dashed line (■) is the hypothetical energy profile in the case of polar stabilization.

These reaction profiles were obtained from full CASSCF optimizations at the aug-cc-pVDZ level using an active space of eight electrons and seven orbitals (π and π^* orbitals of the imine and ketene with the n_σ lone pair of the imine nitrogen).

The energy was corrected by multireference perturbation theory (CASPT2).[10] The calculations were carried out with Gaussian 98[11] and MOLCAS 4.1.[12] All stationary points located were fully optimized and characterized by frequency calculations. CASSCF frequency calculations were also used to add zero point energy (ZPE) values at the CASPT2 energy barriers (see Table 1).

The starting point in the mechanism is the formation of two shallow intermediates having *trans* and *gauche* conformations (**M *trans*** and **M *gauche***, Figure 1), both connected to the reactants through two transition states (the C−N forming bonds are 1.845 and 1.742 Å for the **TS *trans*** and **TS *gauche*** transition states, respectively)

(10) The CASPT2 energy of the ketene reactant has been computed using, for orbital symmetry reasons, a smaller active space of 4 electrons and 3 orbitals.

(11) *Gaussian 98*, revision A.7; M. J. Frisch et al.; Gaussian, Inc.: Pittsburgh, PA, 1998.

(12) *) MOLCAS* Version 4. K. Andersson et al., Lund University, Sweden, 1997.

TABLE 1. Relative Energies (kcal/mol) for the Stationary Points Located on the Potential Energy Surface (PES)[a]

	ΔE^1	ΔE^2
reactants	0.0	0.0
TS *trans*	1.5	3.2
M *trans*	0.3	0.2
TS *gauche*	6.3	7.9
M *gauche*	6.9	8.3
TS1	15.6	19.5
product	−32.5	−31.2

[a] ΔE^1 and ΔE^2 correspond to the CASSCF + ZPE and CASPT2 + ZPE relative energies.

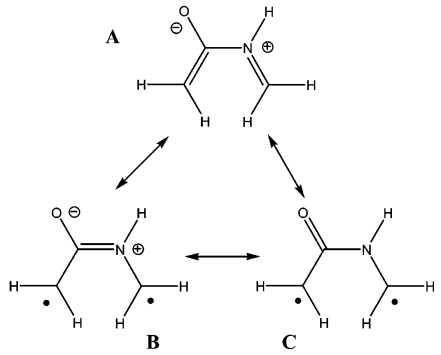
and two electrostatic minima.[13] Meanwhile the *trans* intermediate has a planar transoid butadiene-like structure (*R* is 1.532 Å), the *gauche* intermediate is only hinted at and can be considered simply as a flat zone of the surface. Its instability is indicated by the large distance of the C−N formed bond (1.617 Å). A conrotatory rotation of the two methylene groups connects the *gauche* minimum to the β-lactam through the **TS1** transition state. This transition state shows biradical characteristics and is the combination of some unseparated movements: the rotation around the C−N bond, the formation of the CN double bond, and the reorientation of the two methylene groups. This behavior was confirmed through IRC calculations carried out using an active space of six electrons and six orbitals.

Our gas-phase model shows two important differences with respect to previously reported computational results: (i) Two approaching pathways of the reactants are now detected, *gauche* and *trans*, with the *gauche* transition state being higher in energy by 4.7 kcal/mol. (ii) The *trans* pathway is not an active reaction channel, because it was not possible to find on the PES a pathway connecting the **M *trans*** with the product or with the **M *gauche*** intermediate.

These results, which at first glance seem to complicate the interpretation of the mechanism, confirm that the reaction is very difficult to study at a computational level because the conditions simulated are far from the experimental conditions. It is worthwhile, for example, to remember the dramatic basis set dependence of the number and qualitative nature of the critical points detected in previous computational studies.[14] On the other hand, it is our opinion that the results here obtained are sufficient to understand the real nature of the mechanism.

In our model we are simulating a polar reaction involving the formation of zwitterionic species using a simple gas-phase model. The intermediates are unstable in these conditions where the only stabilizing factor is the π delocalization that reaches the maximum when the systems are planar. Meanwhile the *trans* intermediate has no impediment and the molecule is planar, the *gauche* intermediate, for steric reasons due to the small CĈN angle (111.9° in Figure 2), cannot reach planarity (the dihedral angle is 39.0°). If we make an analogy with

SCHEME 3



the electrocyclic ring closure of *cis*-1,3-butadiene giving cyclobutene, we can show that this planar diene has a CĈC angle of 126.9° at the same computational level (CASSCF/aug-cc-pVDZ). Moreover, when we add correlation and ZPE energies, the *gauche* intermediate becomes higher in energy than the corresponding transition state (**TS *gauche***), making, in fact, the *gauche* approach a single-step process (at CAS-SCF level, without ZPE and correlation energy contributions, **M *gauche*** is 0.19 kcal/mol more stable than **TS *gauche***). For the same reason the *trans* intermediate is not connected to the *gauche* intermediate or consequently to the products. This point is easy to understand if we imagine the rotation around the weak C−N bond, which is, in the case of the **M *gauche***, just hinted at. As the π conjugation decreases, the elongation of the bond occurs, so we have the reactants immediately separated; in fact, it becomes impossible to find a conformational transition state for the rotation around a nonformed bond. This fact avoids the possibility of detecting a pathway connecting the **M *trans*** to the **M *gauche*** (see Figure 2 and Table 1). Moreover, using the resonance structures of Scheme 3, we can introduce, qualitatively, some concepts related to the electronic configurations of the systems we detected using CAS-SCF methods, and that will be the object of further studies.

All structures will be a mixing of these electronic species, where the configurations **A** and **B** are zwitterionic and **B** and **C** diradical. We can guess that **A** and **B** are more important when a polar stabilizing effect (due to the solvent) is present whereas the gas-phase simulation puts emphasis on **C**. In fact, the **M *trans***, which as the result of its planarity has the maximum contribution from all of the configurations, is the more stable intermediate, and **TS1** has geometrical characteristics close to the **C** species. The **M *gauche***, which is not planar and only hinted at, is the consequence of a fragile mixture of the electronic configurations **A**, **B** and **C**.

By taking into account these considerations and the critical points detected here it is now possible to form some hypotheses about the effects of substituents and the presence of a polar solvent on the PES of the reaction.

The presence of a polar solvent or suitable substituents should stabilize the zwitterionic intermediate region more than the transition state zone, thus transforming the energy profile of Figure 2 (dashed line). Now the *trans* pathway is active because **M *gauche*** and **M *trans*** intermediates are interconnected by a conformational transition state. This last result brings us back to the

(13) Electrostatic minima are not discussed here because the CASSCF method provides a poor description of that region of the PES. However, their presence is confirmed by MP2 calculations.

(14) Sordo, J. A.; González, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249.

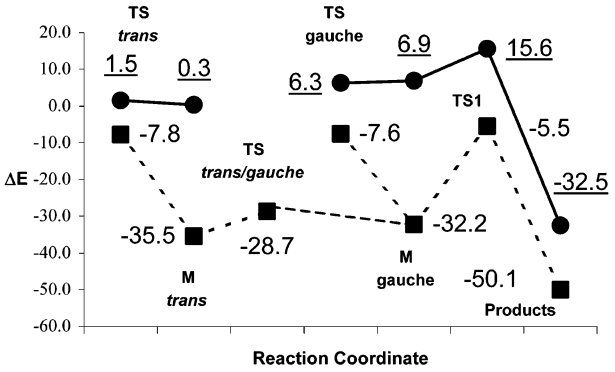
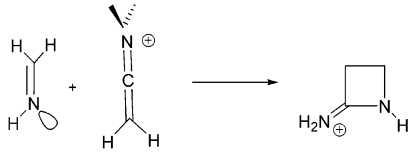


FIGURE 3. Energy profile of the parent ketene + imine reaction (solid line, ●, and underlined numbers) and dashed line (■) for the analogous reaction between parent imine and keteniminium cation. The relative energies (kcal/mol) correspond to the CASSCF (8 electrons, 7 orbitals)/aug-cc-pVDZ + ZPE values.

SCHEME 4



analogy with the electrocyclic ring closure of the 1,3-butadiene to cyclobutene. On this PES, two intermediates, *cis* (or *gauche*) and *trans*, are connected by a conformational transition state and the *cis* intermediate closes in a conrotatory way to give the products.[15]

A good point to support our interpretation comes from the preliminary results of the study of the same mechanism of an analogous reaction: the cycloaddition between imines and keteniminium cations (see Scheme 4), which constitutes an alternative to the Staudinger reaction to yield β-lactams.[16]

In this reaction the intermediate region does not have the same initial destabilizing charge separation present in the ketene + imine reaction. Here, not surprisingly, the CAS-SCF + ZPE results yield the same mechanism and the energy profile is very close to the one we have previously hypothesized in Figure 2 (dashed line). In fact, the stabilization of the intermediate region permits all of the points in PES to be connected, in particular, the **M *trans*** with the **M *gauche***, which now has a completely formed C−N bond of 1.481 Å (see Figure 3).

The last point of our computational study is that other pathways might be competitive. Scanning the whole surface at CASPT2/CASSCF (6 electrons, 5 orbitals)/aug-cc-pVDZ + ZPE level has enabled the transition states for pathway **c** to be detected (Scheme 2). This transition state has an energy of 6.0 kcal/mol higher than **TS1** and is a real biradical system close to the *trans* diradical transistion state of the ethylene + ethylene PES (Figure 4).[17]

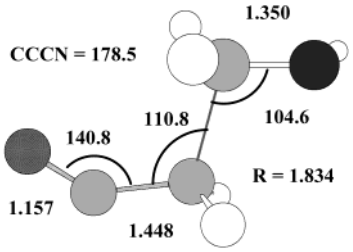


FIGURE 4. Relevant geometrical parameters for the *trans* cc diradical transistion state corresponding to the pathway **c** of Scheme 2. The structure is fully optimized at CASSCF/aug-cc-pVDZ level (6 electrons and 5 orbitals, bond lengths in Å and angles in deg). *R* is the C−C forming bond, and CCNC is the CC(ketene)−CN(imine) dihedral angle.

This result, where the barrier is not far from the rate-determining step of the mechanism here discussed (**TS1**), suggests that the whole potential PES of this reaction can be considered a valid target for further studies. Moreover, these preliminary calculations do not show the presence of other transition states for pathways **1b** and **2**.

Significantly, the presence of two different transition states offers many explanations for the different stereochemical outcome of the reaction. According to previous theoretical studies, in the case of *trans* approach, the stereoselectivity is controlled by the torquoelectronic effect.[8] Also, there are some experimental indications[18] about the fact that the steric requirements of the substituents could influence the stereochemistry of the zwitterionic intermediates involved in the reaction. On the other hand, the *gauche* approach also allows one to consider the interaction between the substituents of the two reactants in the first part of the reaction and to explain some cases of asymmetric induction.[19]

To summarize, the analysis of the results presented here supports the idea that a more complex mechanism may explain the formation of β-lactams from the cycloaddition of ketenes with imines, and in particular, two approaching pathways have now been detected, *gauche* and *trans*.

The more sophisticated description of the PES presented here can be considered a new starting point to rationalize the stereochemical outcome and the solvent effects in these reactions. Interestingly, preliminary calculations on analogous reactions point to the same mechanistic scheme.

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Supporting Information Available: Cartesian coordinates and CASSCF, CASPT2, and ZPE energies of all stationary points optimized and an orbital picture of the CASSCF active space used. This material is available free of charge via the Internet at http://pubs.acs.org.

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