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Role of the Isomerization Pathways in the Staudinger Reaction. A Theoretical Study on the Interaction between Activated Ketenes and Imidates.

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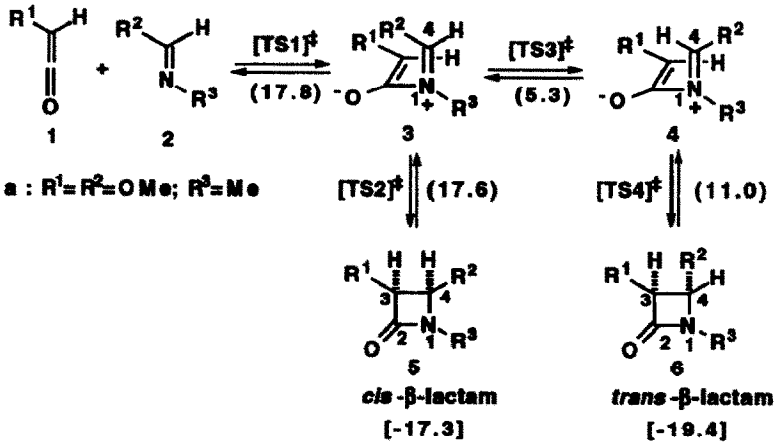
Abstract. Theoretical studies on the Staudinger reaction between methoxyketene and a simple imidate provide an explanation for the *trans* stereoselectivity observed. The key step responsible for this unusual outcome is the facile interconversion between two zwitterionic intermediates through a biradical transition state.

One of the most intriguing features of the Staudinger reaction (SR) between ketenes and imines is the wide range of stereoselectivities observed, depending upon the nature of the substituents and/or the reaction conditions[1]. In view of the importance of this reaction in the chemical synthesis of not only β-lactam antibiotics[2] but also other valuable compounds[3], it is important to improve our knowledge on the diverse reaction paths which can be operating in this atypical cycloaddition. Previous studies[4,5] on the SR have shown that its mechanism involves the intermediacy of zwitterionic intermediates (**3** or **4**, Scheme 1) rather than the direct [2+2] cycloaddition[6] between both reactants (**1** and **2**). A possible explanation[1a,c] for the formation of *cis* and *trans* mixtures of β-lactams **5** and **6** postulates the direct rotation of the N(1)-C(4) bond in **3** to form the isomer **4**. According to this model, the *cis* and *trans* isomers should be formed from the conrotatory electrocyclization of **3** and **4**, respectively. However, in the case of the SR between ketenes and imidates (R^2 = OR, Scheme 1), *trans*-β-lactams are always obtained, regardless of the nature of the remaining substituents[7].



Scheme 1. Numbers in parentheses refer to the AM1 activation enthalpy (kcal/mol) of the corresponding process. Numbers in square brackets are the calculated reaction enthalpies (kcal/mol).

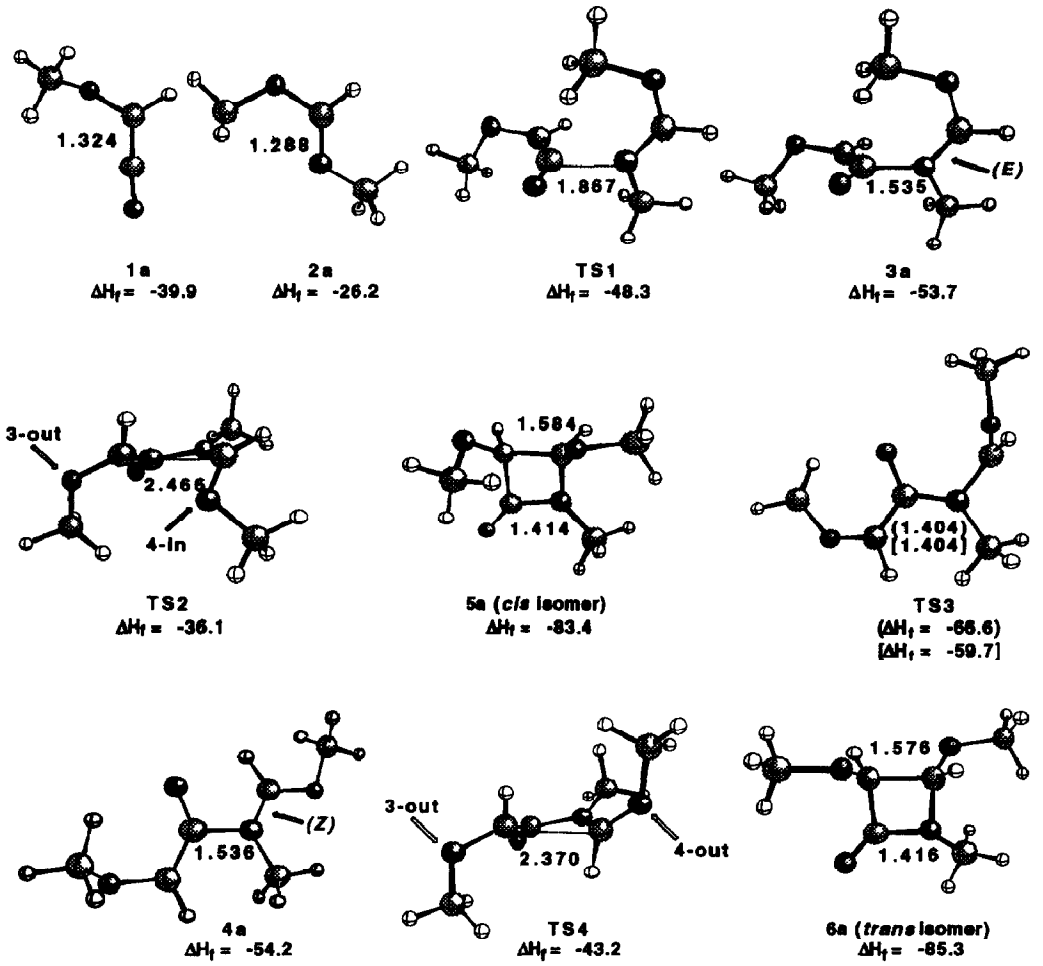


Figure 1. AM1 optimized geometries of the structures **1a-6a** and transition structures **TS1-TS4**. Distances and heats of formation are given in Å and kcal/mol, respectively. Values in brackets and in square brackets correspond to UHF and 3x3CI-HE results, respectively (see text).

We have recently found[4] that the AM1 semi-empirical Hamiltonian[8] provides a satisfactory description of the Staudinger reaction and therefore we decided to extend our study to the interaction between methoxyketene **1a** and (*E*)-*N*-methyl methoxymethylideneamine **2a** to yield the *cis* and/or *trans* 3,4-dimethoxy-1-methylazetidin-2-ones **5a** and **6a**, respectively. These compounds can serve as models for the study of the interaction modes between activated ketenes and imidates.

The stationary points found have been collected in Figure 1. The first step of the reaction consists in the *exo* attack of **2a** over **1a** leading to the formation of the zwitterion **3a** through **TS1**. This transition structure (TS) has a N(1)-C(2) distance of 1.867 Å, and takes place in a non coplanar fashion[9]. The activation enthalpy of this step is of 17.8 kcal/mol. Electrocyclic conrotation of **3a** leads directly to the formation of the *cis*-β-lactam **5a** *via* **TS2**. This TS bears the 3-methoxy group in an outward[10] disposition with respect to the β-lactam ring

in formation, whereas the 4-methoxy group is inward (see Figure 1). The activation enthalpy for this second step is of 17.6 kcal/mol and the reaction enthalpy for the global process (**1a** + **2a** → **5a**) is of -17.3 kcal/mol.

All our attempts to connect the intermediates **3a** and **4a** *via* **TS3** at restricted Hartree-Fock (RHF) level of theory failed. However, when unrestricted Hartree-Fock (UHF) calculations were performed along the reaction coordinate, **TS3** was readily located and characterized. This TS showed only one imaginary frequency in its diagonalized hessian matrix, associated with the rotation around the N(1)-C(4) bond. The dihedral angle formed by the 4-methoxy group and the C(4), N(1) and C(2) atoms was found to be of 92.7° (the corresponding values for **3a** and **4a** are *ca* . 0° and 180°, respectively). This TS exhibited biradical character, with a high spin contamination ($<S^2>$= 1.021 a.u.), thus explaining the difficulties found in its location at the RHF level. In order to characterize **TS3** properly, it was reoptimized using the configuration interaction 3x3CI-half-electron (HE) level of theory as implemented in MOPAC. The geometry thus obtained was almost identical to those found at UHF level, the calculated heat of formation being 6.9 kcal/mol higher. It is well known that semiempirical methods such as AM1 give 3x3CI-HE enthalpies for biradicals that are systematically too negative[11]. In the case of the SR, we have estimated from *ab initio* TCSCF/6-31G* calculations that the enthalpy correction for biradical-like structures is of *ca* .11.3 kcal/mol. This leads to an estimated barrier of 5.3 kcal/mol for the **3a** → **4a** conversion. This value is significantly lower (12.3 kcal/mol) than the activation enthalpy for the **3a** → **5a** transformation, because of the ability of oxygen to stabilize contiguous electron deficient atoms. It is also interesting to note that **4a** is 0.5 kcal/mol more stable than **3a** and its lowest energy conformation is largely different than those of **3a**. Thus, the calculated dihedral angle C(3)-C(2)-N(1)-C(4) for **4a** is of 179.8° (quite similar to those of **TS3**, see Figure 1), whereas for **3a** the value of this dihedral angle is of 107.2°. The electrocyclic conrotation of **4a** leads to the *trans*-β-lactam **6a**, with an activation enthalpy of 11.0 kcal/mol. Therefore, the barrier for this second conrotation is 6.6 kcal/mol lower than those leading to the *cis* cycloadduct **5a**. The reason for this shrink is that **TS4**, which connects **4a** with **6a** *via* **TS4**, has both methoxy groups outward with respect to the β-lactam ring in formation (see Figure 1). Since the torquoelectronic effect operating in electrocyclic conrotatory ring closures[10,4a,5b] favors the outward disposition for donor groups, **TS4** must be of lower energy than **TS2**. Given that the difference in energy between **TS4** and **TS2** is very high and the intermediates **3a** and **4a** are interconvertible through a very low activation barrier, according to our results exclusive formation of the *trans*-β-lactam **6a** should be expected, in full agreement with the experimental evidence. Furthermore, since the reaction enthalpy for the **1a** + **2a** →**6a** process is of -19.4 kcal/mol (1.9 kcal/mol lower than those corresponding to the formation of the *cis*-isomer **5a**), formation of the *trans* cycloadduct is calculated to be favored under both kinetic and thermodynamic control.

In summary, in this study we have shown that the *trans* stereoselectivity observed in the SR between ketenes and imidates can be explained taking into account these two findings: (a) The isomerization around the N(1)-C(4) bond in the intermediates **3** and **4** has a very low activation barrier. The corresponding **TS** should be considered as a biradical (structure **II**, Scheme 2) rather than the zwitterion I usually proposed[1a,c]. (b) The torquoelectronic effect in the second TS favors the formation of the *trans* cycloadduct.

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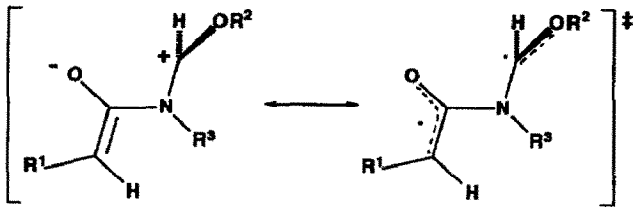

Scheme 2

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