Staudinger Reaction

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On the Stereodivergent Behavior Observed in the Staudinger Reaction between Methoxyketene and (*E*)-*N*-Benzylidenearyl Amines**

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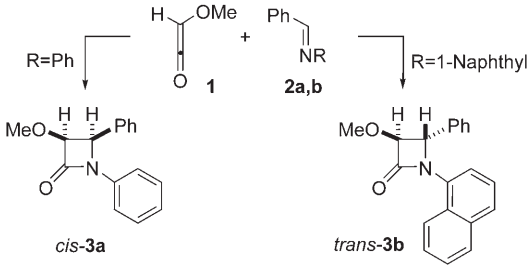
Since its discovery in 1907,[1] the Staudinger reaction between ketenes and imines has been one of the most useful methods for the convergent and stereocontrolled synthesis of β-lactams and other valuable compounds[2] of biological interest. Aside from its practical interest, this reaction is also important from a mechanistic standpoint. As Tidwell[3] stated, "cycloaddition has remained the most distinctive, useful, and intellectually challenging aspect of ketene chemistry."

The Staudinger reaction between ketenes and imines constitutes an example of low-energy [2+2] thermal cycloadditions, a process for which the least motion supra–supra approach is symmetry-forbidden.[4] In fact, in this process the reactants avoid the symmetry-allowed but demanding [$_\pi 2_s + {}_\pi 2_a$] thermal pathway by means of a stepwise mechanism. A major issue of this reaction is the variable sterocontrol achieved that depends upon the nature of the substituents or the reaction conditions.[5,6]

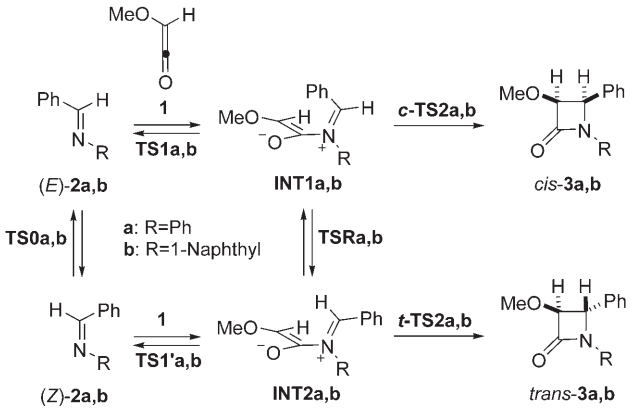
Herein, we present our results on the variability of the sterochemical outcome of the reaction when imines derived from condensed aromatic amines are used. Banik et al.[7] have found that this kind of imine yields exclusively the corresponding *trans*-β-lactams instead of the *cis* cycloadducts usually found in the reaction between alkoxyketenes and imines derived from substituted anilines. A representative example is shown in Scheme 1. These novel β-lactams thus prepared, besides posing a tantalizing mechanistic problem, are potent anticancer compounds.[8] To reproduce the reaction conditions and the geometric features of the substituents, no structural simplifications were introduced.[9,10] Solvent and thermal effects were also considered.[11]



Scheme 1. Stereodivergent outcome observed with differently N-substituted imines. In the case of chiral species, only one enantiomer is shown.

According to the mechanism of the Staudinger reaction, several reaction paths can be envisaged to analyze the sterochemical outcome. Thus, the formation of *cis* cycloadducts **3a**,**b** should take place through direct cyclization of intermediates **INT1a**,**b**. Similarly, the formation of the corresponding *trans* stereoisomers should arise from the conrotatory electrocyclization of zwitterions **INT2a**,**b** (Scheme 2).

As indicated in Scheme 2, intermediates **INT2** can be formed through isomerization of intermediates **INT1** or through isomerization of imines **2** from the *E* to the *Z* configuration. To test this latter hypothesis, several calculations were carried out. According to our results, the isomerization mechanism for this kind of imines consists of the in-plane inversion of the starting imines rather than an out-of-plane rotation.[12] In addition, our calculations on the



Scheme 2. Different reaction paths for the reaction between methoxyketene **1** and imines **2a**,**b** to yield *cis*- and *trans*-3-methoxy-4-phenylazetidin-2-ones (**3a**,**b**). *Exo* attack has been assumed in the first step of the reaction.

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isomerization of imine **2a** show that **TS0a** has aza-allenic character as the *N*-phenyl group is perpendicular to the plane determined by the N=CHPh moiety (Figure 1).

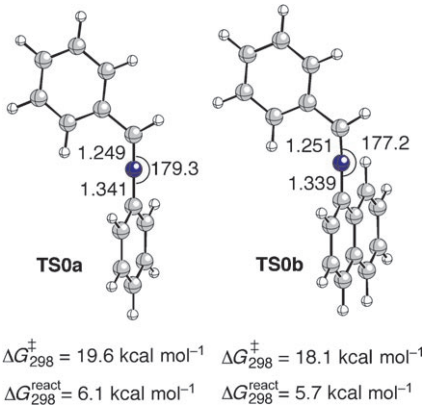

Figure 1. Fully optimized structures of the transition-state structures associated with the *E*→*Z* isomerization of imines (*E*)-**1a**,**b** at the B3LYP(PCM)/6-31+G*//B3LYP(PCM)/6-31G*+ΔZPVE level of theory. Bond lengths [Å] and angles [°] are indicated.

The isomerization profile of imine **2b** is similar to that computed for **2a**, but the activation barrier is 1.5 kcal mol^{-1} lower because of the larger stabilization of **TS0b** induced by the 1-naphthyl moiety.

We next examined the [2+2] cycloaddition reaction leading to β-lactams **3a**,**b**. The computed activation energies for the formation of the N1–C2 bond from ketene **1** and imines (*E*)- and (*Z*)-**2a**,**b** were calculated as indicated in Equations (1) and (2):

$$\Delta G^{\ddagger}_{E} = G_{298}(\mathbf{TS1}) - [G_{298}(\mathbf{1}) + G_{298}((E)\text{-}\mathbf{2})] \quad (1)$$

$$\Delta G^{\ddagger}_{Z} = G_{298}(\mathbf{TS1'}) - [G_{298}(\mathbf{1}) + G_{298}((Z)\text{-}\mathbf{2})] \quad (2)$$

Similarly, the activation energies associated with the formation of *cis*- and *trans*-β-lactams **3a**,**b** through formation of the C3–C4 bonds were computed as indicated in Equations (3) and (4):

$$\Delta G^{\ddagger}_{cis} = G_{298}(\textit{c}\text{-}\mathbf{TS2}) - G_{298}(\mathbf{INT1}) \quad (3)$$

$$\Delta G^{\ddagger}_{trans} = G_{298}(\textit{t}\text{-}\mathbf{TS2}) - G_{298}(\mathbf{INT2}) \quad (4)$$

The free energies of activation corresponding to the isomerization of the zwitterionic intermediates **INT1** and **INT2** by rotation about the N1–C4 bond were computed as indicated in Equation (5):

$$\Delta G^{\ddagger}_{rot} = G_{298}(\textit{c}\text{-}\mathbf{TSR}) - G_{298}(\mathbf{INT1}) \quad (5)$$

Finally, the reaction free energies for the formation of *cis*- and *trans*-β-lactamas **3a**,**b** from ketene **1** and imines **2a**,**b** were computed according to Equations (6) and (7) using the

$$\Delta G^{react}_{cis} = G_{298}(cis\text{-}\mathbf{3}) - [G_{298}(\mathbf{1}) + G_{298}((E)\text{-}\mathbf{2})] \quad (6)$$

$$\Delta G^{react}_{trans} = G_{298}(trans\text{-}\mathbf{3}) - [G_{298}(\mathbf{1}) + G_{298}((E)\text{-}\mathbf{2})] \quad (7)$$

E-imines as a common reference, as these are the major stereoisomers in the two reactions considered. The values obtained for these magnitudes at the 1M standard state (see the Supporting Information)[13] are gathered in Table 1.

Table 1: Activation free energies[a] ($\Delta G^{\ddagger}_{i}$ in kcal mol^{-1}) and reaction free energies[a] (ΔG^{react}_{i} in kcal mol^{-1}) calculated for the reaction between methoxyketene **1** and imines **2a**,**b** to yield β-lactams **3a**,**b**.

ΔG	**1**+**2a**→**3a**	**1**+**2b**→**3b**
$\Delta G^{\ddagger}_{E}$	19.2	20.8
$\Delta G^{\ddagger}_{Z}$	13.7	14.4
$\Delta G^{\ddagger}_{cis}$	1.3	3.6
$\Delta G^{\ddagger}_{trans}$	0.8	0.5
$\Delta G^{\ddagger}_{rot}$	14.4	6.7
ΔG^{react}_{cis}	−16.4	−12.9
ΔG^{react}_{trans}	−18.2	−15.0

[a] Computed by means of Equations (1)–(7) at the B3LYP(PCM)/6-31+G*//B3LYP(PCM)/6-31G*+ΔZPVE level of theory and at the 1 mol L^{-1} standard state.

First, we explored the stepwise formation of cycloadduct *cis*-**3a**. The C–N bond of the 2-azetidinone ring is formed through saddle point **TS1a**, with a C2–N1 distance of approximately 2 Å (Figure 2). The ω angle in this TS indicates an orthogonal attack of the nitrogen lone pair on the sp-hybridized carbon atom of the ketene. The activation free energy for this step is about 19 kcal mol^{-1}, and it is the highest one along the entire [2+2] reaction path (see below). The

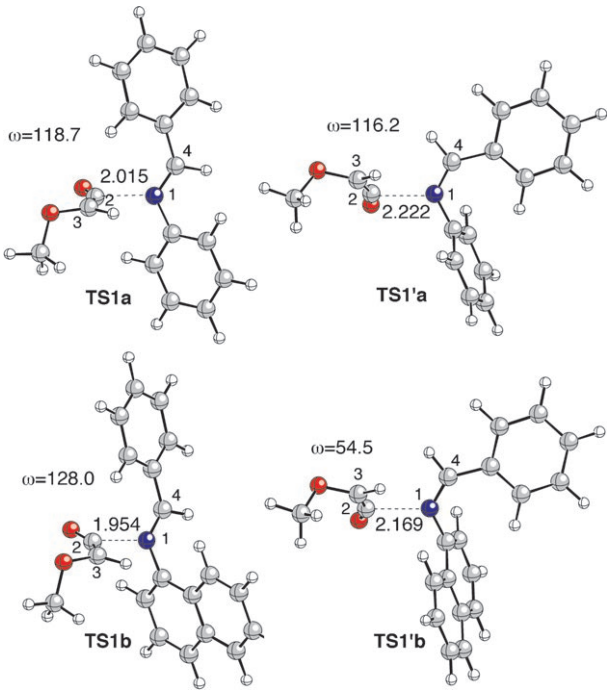

Figure 2. Fully optimized structures of transition-state structures **TS1a**,**b** and **TS1'a**,**b**. The absolute values for the dihedral angles, ω = N1-C2-C3-C4 in degrees, are given. See the caption of Figure 1 for additional details.

zwitterionic intermediate **INT1a** lies only about 3 kcal mol^{-1} below **TS1a**. Conrotatory ring closure of **INT1a** leads to *cis*-**3a** with an activation barrier of only about 1.3 kcal mol^{-1}. The large stabilization of the cycloadduct with respect to the zwitterionic intermediate indicates that this cyclization step can be considered as irreversible (see below). Note that in ***c*-TS2a**, the methoxy group at C3 is in an outward disposition, whereas the phenyl group at C4 occupies the inward position, induced by the *E* geometry of the starting imine **2a** (Figure 4). As the phenyl group is a donor, the torquoelectronic model[14] predicts that an inward-facing phenyl group at C4 introduces a relative destabilization in the transition structure associated with the formation of the C3–C4 bond of the β-lactam ring.

The zwitterionic intermediate **INT2a** can be formed by either rotation about the N1–C4 bond in **INT1a** or nucleophilic attack of imine (*Z*)-**2a** on the sp-hybridized carbon atom of ketene **1**. The corresponding fully optimized saddle points, **TSRa** and **TS1′a** are shown in Figures 2 and 3.

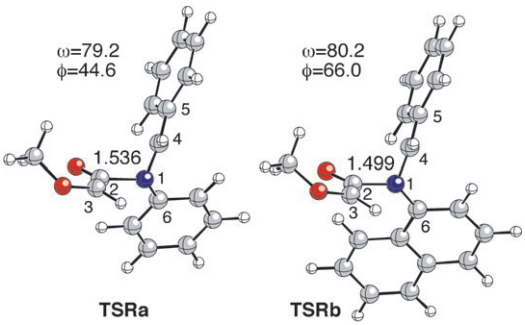

Figure 3. Fully optimized structures of transition-state structures **TSRa**,**b**. The absolute values for the dihedral angles, ω = N1-C2-C3-C4 and ϕ = C6-N1-C4-C5 in degrees, are given. See the caption of Figure 1 for additional details.

According to our results, **TSRa** has an activation barrier that is much larger than those computed for the remaining steps of the entire reaction path.[15] In addition, the activation barrier $\Delta G_Z^{\neq}$ associated with the formation of the C2–N1 bond through interaction between **1** and (*Z*)-**2a** is approximately 5 kcal mol^{-1} lower than that associated with the same step involving (*E*)-**2a**.

The ring-closure step corresponding to the formation of *trans*-**3a** takes place through transition structures ***t*-TS2a** (Figure 4). In this transition state, both the methoxy group at C3 and the phenyl group at C4 occupy outward positions. As a consequence, this latter transition state is around 2.6 kcal mol^{-1} lower in energy than its isomer ***c*-TS2a**. The geometric features of β-lactams *cis*-**3a** and *trans*-**3a** are quite similar. As for the *cis* isomer, the 3-methoxy and 4-phenyl groups are close to each other and this stereoisomer is predicted to be about 5 kcal mol^{-1} less stable than its *trans* congener. Therefore, the experimentally observed formation of *cis*-**3a** must be attributed to kinetic control.

We next performed a similar computational exploration of the reaction paths leading to the formation of β-lactams *cis*- and *trans*-**3b**. The corresponding stationary points are collected in Figures 2, 3, and 4. The general features of these

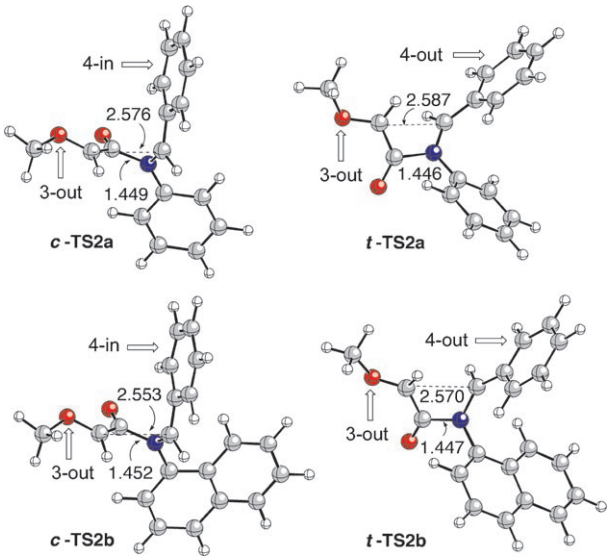

Figure 4. Fully optimized structures of transition structures ***c*-TS2a**,**b** and ***t*-TS1a**,**b**. The arrows labeled 3/4-in/out refer to the inward/outward positioning of the groups in the 3-/4-positions. See the caption of Figure 1 for additional details.

stationary points are very similar to those found in the previous reaction. According to our results, imine (*E*)-**2b** is less nucleophilic than (*E*)-**2a** toward ketene **1** with the corresponding $\Delta G_E^{\neq}$ value being about 1.6 kcal mol^{-1} higher than that found for (*E*)-**2a** (Table 1).

The isomerization from **INT1b** to **INT2b** was calculated to be quite low, about 8 kcal mol^{-1} lower than in the previous case.[15] However, this barrier is significantly higher than those associated with the cyclization step or the cleavage of the N1–C2 bond (**INT** → **2b** + **1** reversal). Conrotatory ring closure of these compounds yields the corresponding *cis*- and *trans*-**3b** cyclaodducts. In this case, ***c*-TS2b** was found to be about 2.6 kcal mol^{-1} less stable than ***t*-TS2b**, thus confirming the destabilizing effect of the inward-facing phenyl group in ***c*-TS2b**. Finally, as in the preceding case, *trans*-**3b** was found to be thermodynamically about 2 kcal mol^{-1} more stable than *cis*-**3b**.

Given the complex nature of these stepwise [2+2] cycloadditions, kinetic analyses of the computed activation energies were carried out. In Figure 5, we report the basic features

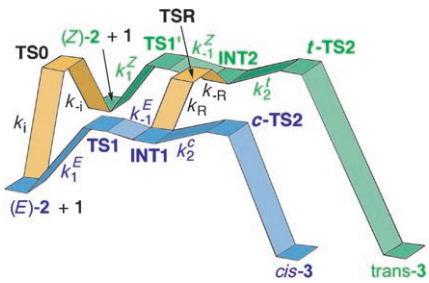

Figure 5. Qualitative diagram showing the different reaction paths and kinetic constants in the Staudinger reaction between ketenes **1** and imines **2** to form *cis*- and *trans*-β-lactams **3**. The subscripts R and i refer to the isomerization of intermediates **INT** and imines **2**, respectively.

of the different reaction profiles for both reactions as well as the notation used in the kinetic treatment of the energetic data reported in Table 1.

As the final steps leading to the β-lactam cycloadducts can be considered irreversible (see above), the formation of the isomeric 2-azetidinones **3a**,**b** can be described by Equations (8) and (9).

$$\frac{d}{dt}[cis\text{-}\mathbf{3}] = k_2^c[\mathbf{INT1}] \tag{8}$$

$$\frac{d}{dt}[trans\text{-}\mathbf{3}] = k_2^t[\mathbf{INT2}] \tag{9}$$

The kinetics describing the evolution of reactants and reaction intermediates is described by means of Equation (10), in which A is the matrix of reactants and reaction intermediates [Eq. (11)] and K is the rate matrix [Eq. (12))].

$$-\frac{d}{dt}A = K\,A \tag{10}$$

$$A = \begin{pmatrix} [(E)\text{-}\mathbf{2}] \\ [(Z)\text{-}\mathbf{2}] \\ [\mathbf{INT1}] \\ [\mathbf{INT2}] \end{pmatrix} \tag{11}$$

$$K = \begin{pmatrix} k_i + k_1^E[\mathbf{1}] & -k_{-i} & -k_{-1}^E & 0 \\ -k_i & k_{-i} + k_1^Z[\mathbf{1}] & 0 & -k_{-1}^Z \\ -k_1^E[\mathbf{1}] & 0 & k_{-1}^E + k_R + k_2^c & -k_{-R} \\ 0 & -k_1^Z[\mathbf{1}] & -k_R & k_{-1}^Z + k_{-R} + k_2^t \end{pmatrix} \tag{12}$$

In Equation (12), the respective rate constants k_n can be estimated from the previously computed activation energies $\Delta G_n^{\ddagger}$ [Eq. (13)], in which k_B and h are the Boltzmann and Planck constants, respectively. The numerical values for these constants can be found in the Supporting Information.

$$k_n = \frac{k_B T}{h}\exp\left(-\frac{\Delta G_n^{\ddagger}}{RT}\right) \tag{13}$$

The reaction between methoxyketene **1** and imine **2a** to yield β-lactams **3a** was analyzed first. Numerical integration of Equations (8)–(10) with time yielded the almost exclusive formation of cycloadduct *cis*-**3a** (> 98 % *de*, see Figure 6a), in excellent agreement with the experimental evidence. The reasons for this outcome lie in the relatively high *E*/*Z* isomerization barriers for both isomers of imine **2a** and intermediates **INT1a** and **INT2a**.

In contrast, when the same treatment was applied to the Staudinger reaction between methoxyketene **1** and imine (*E*)-**2b**, the reverse stereochemical outcome, namely the preferred formation of β-lactam *trans*-**3b**, was obtained, with a calculated diasteromeric excess of about 94 % (Figure 6b). This result is also in excellent agreement with the experimental results.[7,16] This reversal in the stereoselectivety lies in the isomerization steps prior to the cycloaddition stages. In the case of imines derived form N-polycyclic arenes, the aromatic rings stabilize the corresponding transition states of type **TS0**. The second key aspect is that *E*-imines are less nucleophilic than their *Z* congeners, because of the larger steric hindrance induced by the arylidene group. Note also that the isomerization of the zwitterionic intermediates **INT1** by rotation about the N1–C4 moiety does not appear to play any significant role in the stereochemical outcome of these particular reactions. Suppression of the **INT1**⇄**INT2** routes by making $k_R = k_{-R} = 0$ resulted in profiles identical to those reported in Figure 6.

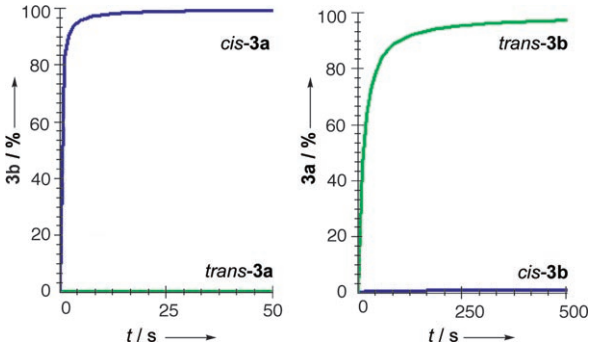

Figure 6. Simulated stereochemical outcome associated with the reaction between methoxyketene **1** and imines (*E*)-**2a**,**b**. This distribution of isomers was obtained from Equations (8)–(13).

In summary, our results indicate that the stereochemistry of these reactions is a consequence of the balance between the activation energy associated with the isomerization of the starting *E*-imine and the energy barrier corresponding to the formation of the N1–C2 bond: If the former barrier is lower than the latter, the *trans* cycloadduct will be the major stereoisomer, otherwise preferential or exclusive formation of *cis*-β-lactams will be observed.

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[15] UB3LYP(PCM) calculations indicate that these reaction intermediates and transition structures have zwitterionic character.

[16] The critical concentration of ketene **1** required to revert this situation would be $[\mathbf{1}]_c \approx k_i/k_{\mathbf{1}}^E = 82\ \mathrm{mol\,L^{-1}}$ in the case of imine (*E*)-**2b**, probably a value too large to be reproduced experimentally.

