Theoretical Study of the [2+2] Cycloaddition of Thioketenes with Imines To Form β-Thiolactams

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Abstract: The cycloaddition reaction of thioketene with formaldimine was investigated by ab initio (HF/6-31 G* and MP2/6-31 G*) and DFT (B3LYP/6-31 G*) methods. The electrostatic effect of solvent was taken into account at the HF/6-31 G* and MP2/6-31 G*//HF/6-31 G* SCRF levels of theory. In the gas phase, three mechanisms were found at each level of theory, while in solution four mechanisms were obtained. The most favorable mechanisms, both in the gas phase and in solution, correspond to two- and three-step processes which have in common a conrotatory electrocyclic closure to give the 2-thioazetidinone. *Gauche* and *trans* zwitterionic intermediates play a fundamental role in the stepwise mechanisms for this process. The calculated free-energy barrier in the gas phase was 33.0 kcal mol^{-1}, while in solution the corresponding values were 28.9 and 26.8 kcal mol^{-1} for anisole ($\varepsilon = 4.33$) and *N*,*N*-dimethylformamide ($\varepsilon = 37.0$) solvents, respectively. In agreement with experimental findings, our calculations showed that the rate of this reaction is not very sensitive to solvent polarity. According to MP2/6-31 G*//HF/6-31 G* calculations, the effect of monosubstitution in thioketene (R = OH, CH_3, or CHO) was in accordance with the torquoelectronic rule defined by Houk, which predicts that donor and acceptor substituents favor the *outward* and *inward* orientations, respectively. In order to model the experimental systems more closely, the reaction of isopropyl-*tert*-butylthioketene with *N*-(benzylidene)methylamine, Me–N=CH(Ph) was investigated at the HF/6-31 G*//HF/3-21G* level. In contrast to previous interpretations based on steric effects, our results explain the most favorable *trans* relationship of the two most bulky substituents in the product in terms of electronic effects.

Keywords: ab initio calculations · cycloadditions · lactams · solvent effects · torquoelectronic effects

Introduction

The [2+2] cycloaddition reactions are a useful method for the synthesis of cyclic compounds.[1] Among the most interesting reactions of this type are those involving ketenes as one of the 2π components. Two examples of this class of cycloadditions are the reactions of ketene with alkenes and imines to give cyclobutanones and β-lactams, respectively.[2]

The [2+2] cycloaddition of thioketenes with azomethines has been reported as a synthetic route to β-thiolactams.[3] Recently, the conversion of the β-thiolactams to the biologically and clinically interesting β-lactams has been shown to be a simple procedure in most cases.[4] This constitutes a novel route to β-lactams and has led to renewed interest in the chemistry of β-thiolactams.

Experimental results have shown that reactions of unsymmetrically substituted thioketenes are only poorly stereoselective. Two mechanisms are considered possible for this reaction: a synchronous concerted process and a stepwise process via a dipolar intermediate. Kinetic measurements have revealed no significant solvent dependence of the rate of cycloaddition, in contrast to the reaction between ketenes and azomethines, and the analysis of products revealed no 2:1 adduct corresponding to a 1,4-dipolar cycloaddition of the reactants to the hypothetical intermediate. In spite of this evidence, a concerted mechanism for this reaction is not regarded as conclusively proven, since the cancellation of enthalpic and entropic factors, as well as steric hindrance, could hide the presence of the dipolar intermediate, which, on the other hand, would allow some experimental findings to be rationalized.[3]

The stepwise mechanisms of the ketene–imine [2+2] cycloaddition reaction have been supported by theoretical and experimental evidence. Recent theoretical studies[5,6] indicate that ketenes and imines react in a nonconcerted

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process, with formation of a zwitterionic intermediate, which undergoes an electrocyclic conrotatory closure to give the final β-lactams. However, to our knowledge, theoretical studies of the reactions between thioketenes and imines have not been reported. Therefore, we undertook a theoretical study of the mechanism of the [2+2] cycloaddition of thioketenes and imines in order to investigate the existence of an intermediate and to clarify its role in the reaction mechanism. The effect of solvents of various polarities and of substitution in thioketene and formaldimine were taken into account.

Methods of Calculation

Quantum-chemical calculations were carried out with the Gaussian 92/DFT system of programs[7] with addition of extra links for the treatment of solvent effects.[8] In the gas phase, stable structures were fully optimized and transition structures were located by Schlegel algorithm[9] at the HF, MP2 and DFT (B3LYP[10]) levels by using the 6-31G* basis set.[11] Harmonic vibrational frequencies were calculated at all theory levels to characterize the critical points and to evaluate the zero-point vibrational energies (ZPVE). Single-point MP4SDTQ(FC)/6-31G* calculations were carried out on MP2(FC)/6-31G* geometries.

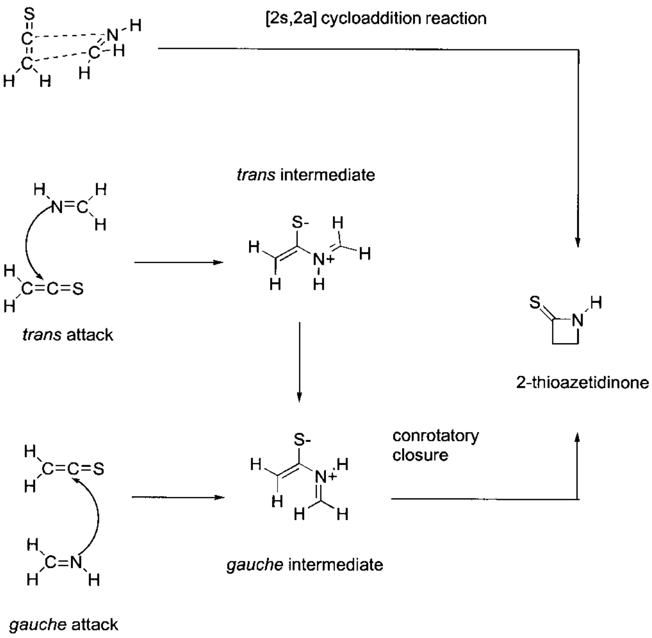
Enthalpy, entropy, and free-energy values were calculated to obtain results more readily comparable with experiment. These quantities were computed within the ideal-gas, rigid-rotor, and harmonic-oscillator approximations.[12] A temperature of 298.15 K and a pressure of 1 atm were used in the calculations.

In solution, full-geometry optimizations were carried out at the HF/6-31G* level, and single-point MP2/6-31G* calculations were performed on the HF geometries. A general SCRF model proposed for quantum-chemical computations on solvated molecules was used.[13] The solvent is represented by a continuum that is characterized by its relative static dielectric permittivity ε. The solute, which is located in a cavity created in the continuum by the release of cavitational energy, polarizes the continuum, and this in turn creates an electric field inside the cavity. Once equilibrium is reached, the electrostatic part of the free energy of the solvation process is obtained by a monocentric multipolar expansion of the molecular charge distribution.[14] The SCRF continuum model employed assumes a general cavity shape, which is obtained by using solute atomic spheres whose van der Waals radii are modified to fulfil the volume condition ($1.3084\,r_{vdW}$).[13a] Relative permittivity values of 4.33 and 37.0 were considered to simulate anisole and *N*,*N*-dimethylformamide, respectively, which were used as solvents in the experimental work.[3]

Results and Discussion

Reaction mechanisms in vacuo: Three different mechanisms were found for the cycloaddition of thioketene with formaldimine at all the theory levels used in this work (see Scheme 1 and Figure 1). The geometries of the critical structures located are displayed in Figure 2. The relative energies for these structures at the different theory levels are collected in Table 1. Unless otherwise stated the energies referred to in the text are those corresponding to the highest theory level used in the present work, MP4/6-31G*//MP2/6-31G*, without the ZPVE correction.

The first mechanism is concerted and passes through a highly asynchronous [2s,2a] transition state **TS**$_\mathbf{d}$, with an energy barrier of 36.8 kcal mol^{-1}. This is analogous to the disrotatory mechanism described previously for the reactions of ketene[15] and fluoroketene[5f] with imines. However, the corresponding transition states exhibit some differences. On the one hand, C(thioketene)–N bond formation in **TS**$_\mathbf{d}$ (see Figure 2) is more advanced than in the analogous transition states for the disrotatory addition of ketene to imine and the *anti* addition of fluoroketene to imine. On the other hand, although the C(thioketene)–N distance in **TS**$_\mathbf{d}$ is similar to



Scheme 1. Three different mechanisms for the cycloaddition of thioketene with formaldimine.

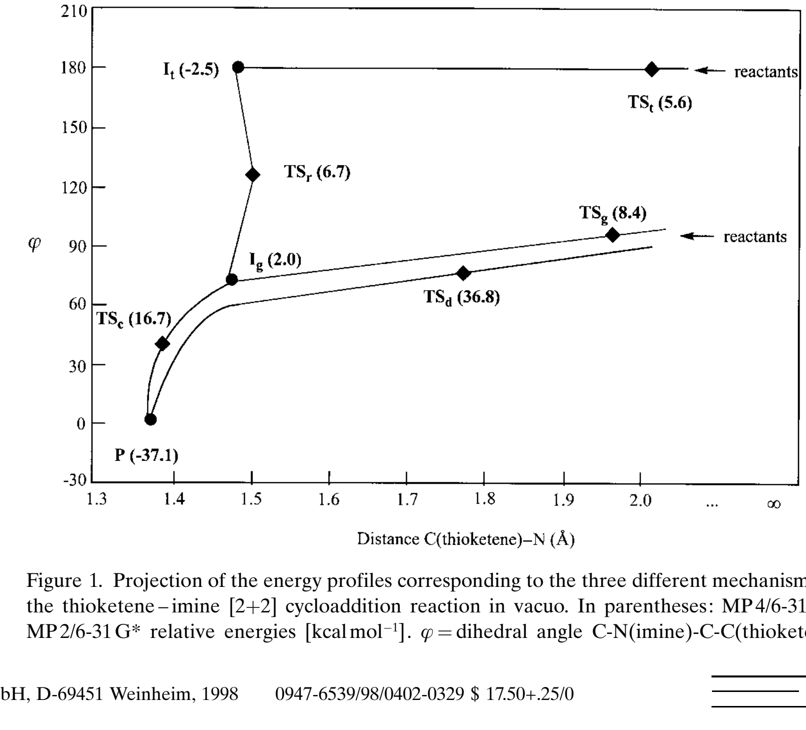


Figure 1. Projection of the energy profiles corresponding to the three different mechanisms for the thioketene–imine [2+2] cycloaddition reaction in vacuo. In parentheses: MP4/6-31G*//MP2/6-31G* relative energies [kcal mol^{-1}]. φ = dihedral angle C-N(imine)-C-C(thioketene).

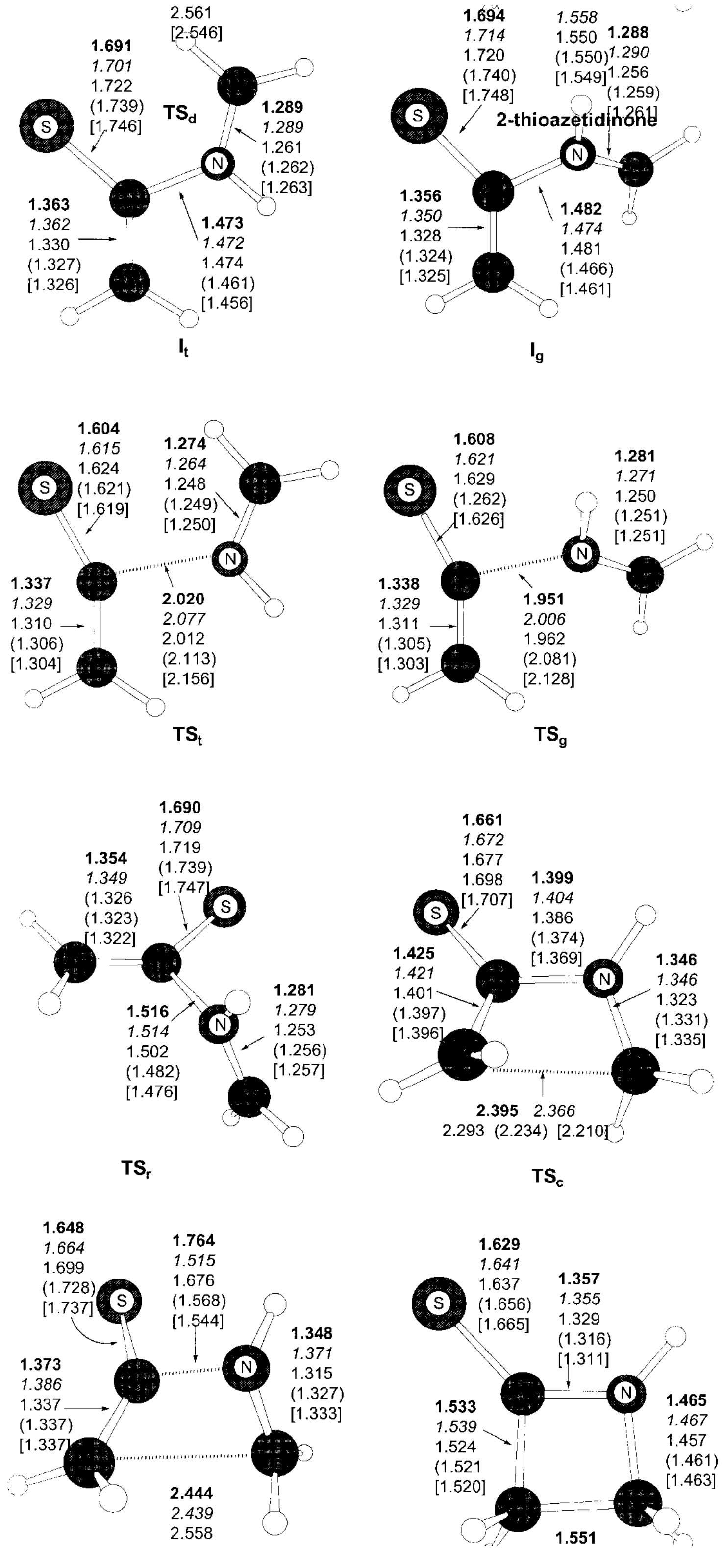


Figure 2. Optimized geometries of the most important structures located in the gas phase and in solution for the [2+2] cycloaddition reaction of thioketene with imine. Distances in Å, bold: MP2; italic: B3LYP; Roman: HF; in parentheses: HF SCRF $\varepsilon = 4.33$; in square brackets: HF SCRF $\varepsilon = 37.0$.

that in the transition state for the disrotatory closure in the *syn* addition of fluoroketene to imine, $\mathbf{TS_d}$ corresponds to a concerted process according to intrinsic reaction cocordinate calculations.[16] Interestingly, $\mathbf{TS_d}$ is the structure most sensitive to the theory level used. With the DFT method this transition state presents a more asynchronous structure and a lower energy barrier compared to the other methods. Nevertheless, the concerted mechanism is the least favorable according to all the methods employed (see Table 1).

The second mechanism is a three-step process that corresponds to the nucleophilic *trans* attack of formaldimine on thioketene. This reaction path passes through a planar transition state $\mathbf{TS_t}$, with an energy barrier of 5.6 kcal mol^{-1}, and leads to a planar zwitterionic intermediate $\mathbf{I_t}$, which is 2.5 kcal mol^{-1} more stable than the reactants. Intermediate $\mathbf{I_t}$ evolves by internal rotation about the C(thioketene)–N bond (see Figure 2) through a transition state $\mathbf{TS_r}$, 9.2 kcal mol^{-1} higher in energy, to give intermediate $\mathbf{I_g}$, which is 4.5 kcal mol^{-1} less stable than $\mathbf{I_t}$ and 2.0 kcal mol^{-1} less stable than the reactants. Finally, a transition state $\mathbf{TS_c}$, corresponding to the conrotatory electrocyclic closure of $\mathbf{I_g}$ and 19.2 kcal mol^{-1} less stable than $\mathbf{I_t}$, leads to the product, 2-thioazetidinone. This third step has the highest energy barrier.

The third mechanism is a two-step process that first passes through a *gauche* transition state $\mathbf{TS_g}$, which is 8.4 kcal mol^{-1} less stable than the reactants, and leads to the *gauche* intermediate $\mathbf{I_g}$, which gives the final product via $\mathbf{TS_c}$, which lies 16.7 kcal mol^{-1} above the reactants. This third mechanism has the conrotatory electrocyclic closure of $\mathbf{I_g}$ in common with the second mechanism. The energy of reaction is -37.1 kcal mol^{-1}, similar to that of the Staudinger reaction.[5a]

Both ab initio and B3LYP methods give the same topology for this gas-phase potential energy surface. The *trans* and *gauche* intermediates occur as stable structures on this potential energy surface, in contrast with the ketene–imine cycloaddition reaction, for which only the *trans* intermediate was located.[5a,5c] The strong donor–acceptor interaction between fragments in these intermediates is reflected in the C(thioketene)–N distances (1.47–1.48 Å), which are close to typical C–N bond lengths. A configurational analysis[17] shows that in the case of thioketene, local excitation from the next HOMO to the antibonding orbital of the C=S bond is much more important than in ketene,[5b,5c] which reflects the greater polarizability of the former and explains then the higher stability of the corresponding zwitterionic intermediates. The MP2 and B3LYP geometries and relative energies are very similar, except for the concerted mechanism, for which the energy barrier is 34.0 and 29.7 kcal mol^{-1} according to MP2 and B3LYP methods, respectively. Single-point MP4 calculations on the MP2 geometries give relative energies 3–4 kcal mol^{-1} above the MP2 values (see Table 1).

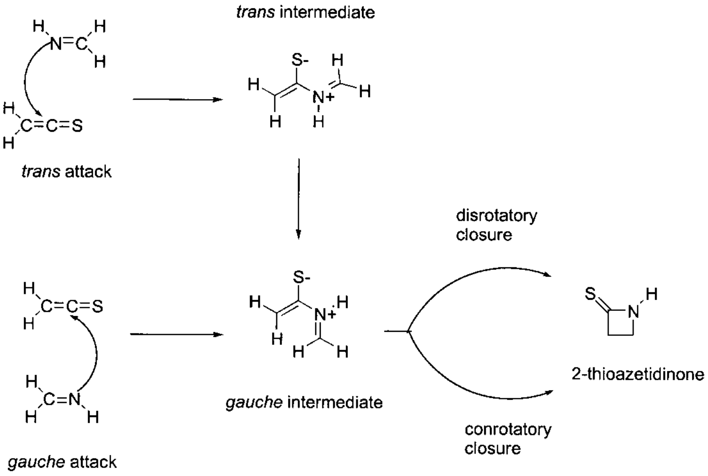
Table 1. Relative energies (kcal mol^{-1}) for the chemically important structures in the thioketene–formaldimine cycloaddition reaction in a vacuum at the various theory levels used in this work.

Structures	HF/6-31 G*[a]	MP2/6-31 G*// HF/6-31 G*	MP2/6-31 G*[a]	MP4/6-31 G*// MP2/6-31 G*	B3LYP/6-31 G*[a]
intermediates					
$\mathbf{I}_\mathrm{t}$	– 2.1 (5.3)	– 4.9	– 5.3 (4.4)	– 2.5	– 6.7 (4.4)
$\mathbf{I}_\mathrm{g}$	– 2.6 (5.1)	– 0.6	– 1.0 (4.3)	2.0	– 2.9 (4.3)
transition states					
$\mathbf{TS}_\mathrm{t}$	11.7 (2.6)	5.0	4.7 (2.2)	5.6	4.3 (2.2)
$\mathbf{TS}_\mathrm{g}$	14.0 (2.5)	7.7	7.3 (2.2)	8.4	6.2 (2.2)
$\mathbf{TS}_\mathrm{r}$	5.9 (4.7)	4.0	3.8 (4.0)	6.7	3.7 (3.8)
$\mathbf{TS}_\mathrm{c}$	29.3 (4.2)	13.3	13.4 (3.7)	16.7	13.7 (3.7)
$\mathbf{TS}_\mathrm{d}$	43.3 (3.2)	35.6	34.0 (2.7)	36.8	29.7 (3.1)
product					
2-thioazetidinone	– 39.9 (6.3)	– 42.8	– 42.1 (6.1)	– 37.1	– 38.1 (5.9)

[a] ZPVE correction to relative energies in parentheses.

Table 2 summarizes the various contributions to ΔG for the above three mechanisms in the gas phase. The energy barriers are augmented by an entropic contribution in all cases. Intermediates $\mathbf{I}_\mathrm{t}$ and $\mathbf{I}_\mathrm{g}$ are 14.3 and 18.5 kcal mol^{-1} less stable than the reactants on the free energy PES. The two- and three-step mechanisms are equally favorable since the rate-determining step in both cases is conrotatory electrocyclic closure, with a free-energy barrier of 33.0 kcal mol^{-1}. The concerted mechanism is again the least favorable, with a free-energy barrier of 51.8 kcal mol^{-1}. The free energy of reaction is –18.6 kcal mol^{-1}.

Reaction mechanisms in solution: Figure 2 also shows the geometrical parameters of the HF/6-31 G* SCRF optimized structures for the addition of thioketene to imine in anisole and *N,N*-dimethylformamide. Table 2 lists the corresponding relative electrostatic free energies of solvation and free energies in solution. The inclusion of solvent effects leads to four different reaction mechanisms (see Scheme 2). Two approaches (*trans* and *gauche*) of the reactants are possible, and these converge into the *gauche* intermediate $\mathbf{I}_\mathrm{g}$. This *gauche* intermediate can evolve through conrotatory or disrotatory closure to give the product.



Scheme 2. The inclusion of solvent effects results in two possible closure mechanisms for the *gauche* intermediate.

In solution $\mathbf{TS}_\mathrm{t}$ and $\mathbf{TS}_\mathrm{g}$ have a longer C(thioketene)–N bond (by about 0.1 Å) than in the gas phase, while the geometries of intermediates $\mathbf{I}_\mathrm{t}$ and $\mathbf{I}_\mathrm{g}$ and the transition state $\mathbf{TS}_\mathrm{r}$ are less sensitive to the electrostatic effect of solvent and exhibit a moderately shorter C(thioketene)–N distance (by 0.01–0.02 Å) compared to the analogous gas-phase structures (see Figure 2). In general the presence of solvent stabilizes all the structures along the reaction mechanisms with respect to reactants; the greater the polarity of solvent the greater the stabilization (Table 2). A preferential stabilization takes place

Table 2. Relative thermodynamic energies (kcal mol^{-1}) for the chemically important structures in the thioketene–formaldimine cycloaddition reaction. Relative electrostatic free energies (kcal mol^{-1}) of solvation ($\delta\Delta G^\mathrm{elec}_\mathrm{solv}$) in anisole ($\varepsilon = 4.33$) and *N,N*-dimethylformamide ($\varepsilon = 37.0$) solvents are also shown.

Structures	ΔH[a]	$T\Delta S$[a]	$\Delta G_\text{gas-phase}$	$\delta\Delta G^\mathrm{elec}_\mathrm{solv}$[b] $\varepsilon = 4.33$	$\delta\Delta G^\mathrm{elec}_\mathrm{solv}$[b] $\varepsilon = 37.0$	ΔG[c] $\varepsilon = 4.33$	ΔG[c] $\varepsilon = 37.0$
intermediates							
$\mathbf{I}_\mathrm{t}$	1.6	– 12.7	14.3	– 8.2 (– 10.5)	– 12.2 (– 15.0)	6.1	2.1
$\mathbf{I}_\mathrm{g}$	6.2	– 12.3	18.5	– 8.9 (– 11.9)	– 13.2 (– 17.0)	9.6	5.3
transition states							
$\mathbf{TS}_\mathrm{t}$	7.9	– 11.7	19.6	– 1.4 (– 2.3)	– 1.7 (– 2.9)	18.2	17.9
$\mathbf{TS}_\mathrm{g}$	10.8	– 11.4	22.2	– 1.5 (– 2.8)	– 1.9 (– 3.6)	20.7	20.3
$\mathbf{TS}_\mathrm{r}$	10.2	– 13.0	23.2	– 9.7 (– 12.1)	– 7.2 (– 17.3)	13.5	16.0
$\mathbf{TS}_\mathrm{c}$	19.9	– 13.1	33.0	– 4.1 (– 6.9)	– 6.2 (– 9.9)	28.9	26.8
$\mathbf{TS}_\mathrm{d}$	39.4	– 12.4	51.8	– 1.9 (– 6.5)	– 3.7 (– 9.7)	49.9	48.1
product							
2-thioazetidinone	– 31.5	– 12.9	– 18.6	– 1.4 (– 2.2)	– 2.1 (– 3.2)	– 20.0	– 20.7

[a] 298.15 K, 1 atm. Thermal and ZPVE energies were obtained from the MP2/6-31 G* frequencies, while electronic contributions were derived from the MP4/6-31 G*//MP2/6-31 G* single-point calculations. [b] MP2/6-31 G*//HF/6-31 G* SCRF calculations (HF/6-31 G* SCRF values in parentheses). [c] $\Delta G_\text{gas-phase} + \delta\Delta G^\mathrm{elec}_\mathrm{solv}$ (MP2//HF).

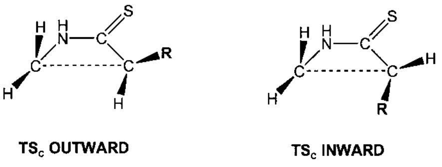
in the case of the zwitterionic structures $\mathbf{I}_t$, $\mathbf{I}_g$, and $\mathbf{TS}_r$, and to a lesser extent for $\mathbf{TS}_c$ and $\mathbf{TS}_d$. According to the free energy in solution, the *trans* and *gauche* approaches that lead to the final product through a conrotatory closure are the most favorable. They have in common the rate-determining step of the process $\mathbf{TS}_c$, with an energy barrier of 28.9 and 26.8 kcal mol^{-1} for anisole and *N*,*N*-dimethylformamide, respectively. The disrotatory mechanism[5f] connecting the *gauche* intermediate with 2-thioazetidinone has a free energy barrier of 49.9 and 48.1 kcal mol^{-1}, respectively, for the two solvents. According to our calculations, the free energy of reaction is −20.0 and −20.7 kcal mol^{-1} in anisole and *N*,*N*-dimethylformamide, respectively.

It has been reported that the rate of this reaction is not very sensitive to solvent polarity.[3] This trend is reflected in our calculations, since for the thioketene–imine addition the highest energy barrier is lowered by 3.0 kcal mol^{-1} at the HF/6-31G* SCRF level on changing from anisole to *N*,*N*-dimethylformamide, whereas at the MP2/6-31G*//HF/6-31G* SCRF level the corresponding decrease is 2.1 kcal mol^{-1}. Furthermore, the presence of substituents tends to attenuate the effect of solvent polarity (see below).

Effect of substituents: In order to understand the effect of substituents on the rate-determining transition state for conrotatory closure to give the *β*-thiolactam product, we studied the influence of three substituents (OH, CH_3, and CHO) in thioketene and the reaction between isopropyl-*tert*-butylthioketene and *N*-(benzylidene)methylamine.

The stereochemical role of monosubstitution in thioketene was investigated at the MP2/6-31G*//HF/6-31G* level in the gas phase and in solution. Table 3 presents the corresponding relative energies between the *outward* and *inward* transition states. These results are in agreement with the torquoelectronic effect defined by Houk,[18] according to which an inwardly oriented, filled substituent donor orbital would overlap with the σ_{CC} MO of the newly forming C–C bond to give a destabilizing cyclic four-electron interaction, whereas in *outward* orientation it would overlap with the antibonding σ^*_{CC} MO through a two-electron stabilizing interaction. Conversely, an inwardly oriented, vacant substituent acceptor orbital would undergo a stabilizing interaction with the σ_{CC} MO. With the strongest donor substituent (R = OH), the most favorable transition state corresponds to *outward* electrocylic closure, with a considerable energy difference of 21.2 kcal mol^{-1} (see Table 3). With a milder donor (R = CH_3), the *outward* orientation remains more favorable than the *inward* one, but the difference between them is reduced to 8.3 kcal mol^{-1}. Finally, the role of a mild acceptor substituent was studied by using the CHO group in which the oxygen atom resides in a *syn* orientation with respect to the hydrogen substituent of the terminal C atom of thioketene. MP2/6-31G*//HF/6-31G* calculations in the gas phase predict that the *inward* transition state is favored by 3.0 kcal mol^{-1}.

Table 3. Relative energies (kcal mol^{-1}) between the *inward* and *outward* transition structures corresponding to the conrotatory electrocyclic closure step in the cycloaddition reaction between formaldimine and substituted thioketenes. Structures were optimized at the HF/6-31G* theory level in gas phase and at the HF/6-31G* SCRF level in solution.



$\mathbf{TS_c}$ **OUTWARD** $\mathbf{TS_c}$ **INWARD**

	HF/6-31G* gas-phase	ZPVE[a] gas-phase	MP2/6-31G*//HF/6-31G* gas-phase	solution $\varepsilon = 4.33$	solution $\varepsilon = 37.0$
R = OH	23.4	−0.8	21.2	20.5	19.9
R = CH_3	9.2	0.3	8.3	7.8	7.6
R = CHO	0.3	0.4	−3.0	−3.0	−3.4

[a] ZPVE correction from HF/6-31G* frequencies.

The electrostatic effect of solvent on the calculated torquoselectivity consists of a slight diminution of the energy difference between *inward* and *outward* structures for the donor substituents. Remarkably, these energy differences are scarcely sensitive to solvent polarity. On passing from a dielectric constant of 4.33 to 37.0, the energy difference between the *inward* and *outward* transition states changes by only 0.6, 0.2, and −0.4 kcal mol^{-1} for the OH-, CH_3-, and CHO-substituted structures, respectively (see Table 3).

In order to model more closely the systems studied experimentally, the stereoselectivity of this class of reactions was investigated by optimizing the conrotatory transition states for the reaction of isopropyl-*tert*-butylthioketene with *N*-(benzylidene)methylamine. Given the size of these systems, single-point calculations were carried out at the HF/6-31G* and B3LYP/6-31G* theory levels in the gas phase and at the HF/6-31G* SCRF level in solution on the HF/6-31G* geometries. The four stereoisomers of the transition state are shown in Figure 3, which includes the relative energies with respect to the most favorable transition state.

In the gas phase the most favorable structure is **TS2**, in which the *tert*-butyl and phenyl substituents are in *outward* orientation. This **TS2** presents the most advanced formation of the new C–C bond. Transition states **TS1** and **TS4**, in which the phenyl and *tert*-butyl groups have a *cis* arrangement are 5.4 and 5.2 kcal mol^{-1} less stable than **TS2**, respectively. In **TS1** the *tert*-butyl group is outwardly oriented, while in **TS4** it is in *inward* orientation. The least stable transition state is **TS3** (13.2 kcal mol^{-1} less stable than **TS2**) in spite of its having the two bulkiest substituents in a *trans* arrangement. Both bulky substituents (*tert*-butyl and phenyl) are in *inward* orientation. The relative stability of **TS1**–**TS4** can be rationalized in terms of electronic effects. Thus, in accordance with the torquoselectivity concept, the most stable transition state, **TS2**, has the donor groups in *outward* orientations, whereas the least stable, **TS3**, has these groups in *inward* orientations. The transition states of intermediate stability have one of the donor groups in *inward* orientation and the other in *outward* orientation.

The electrostatic effect of solvent on the stability of **TS1**–**TS4** is moderate, the most remarkable feature being the reduction of the energy difference between **TS2** and **TS4** to 3.2 kcal mol^{-1} (Figure 3). The inclusion of correlation energy

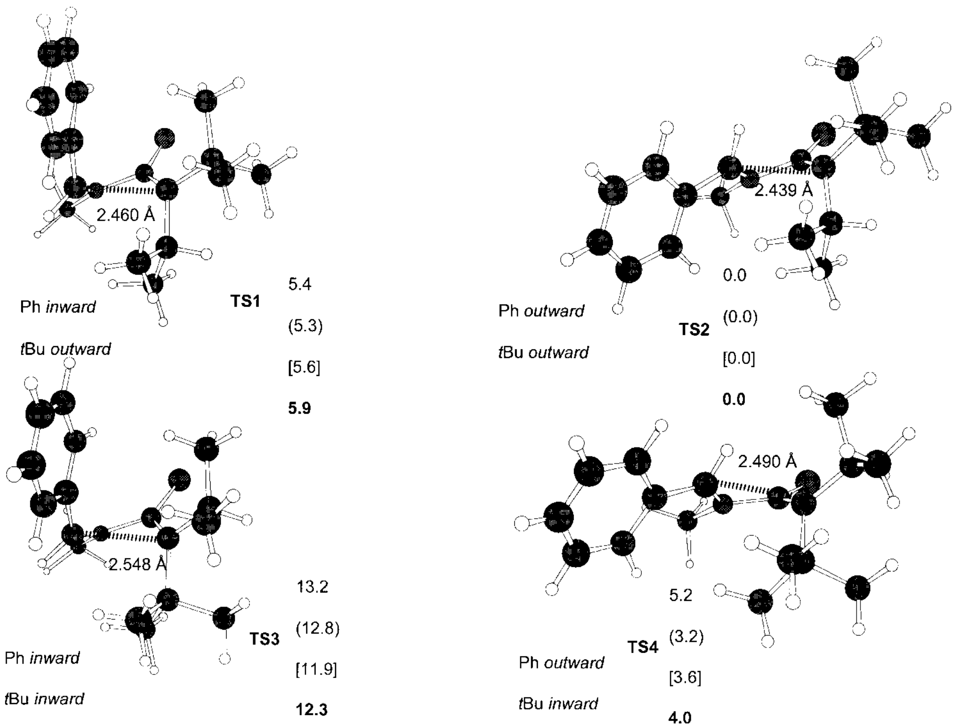


Figure 3. HF/6-31 G* optimized structures of the conrotatory transition states for the reaction of isopropyl-*tert*-butylthioketene with *N*-(benzylidene)methylamine. Distances in Å; relative energies in kcal mol^{-1}; Roman HF/6-31G*; in parentheses HF/6-31G* SCRF $\varepsilon = 4.33$; in square brackets HF/6-31G* SCRF $\varepsilon = 37.0$; bold: B3LYP/6-31G*.

at the B3LYP/6-31G* level tends to lower this energy difference even further to 1.2 kcal mol^{-1} (Figure 3). Thus although **TS2** remains the most stable transition state in solution, the energy difference between **TS2** and **TS4** is not large. This is in agreement with the experimental finding that the major product has the bulkiest groups in a *trans* arrangement, and that the reaction is only poorly stereoselective.[3] However, in contrast with previous interpretations, which explain these results in terms of steric effects, our calculations reveal electronic effects to be the most important factor determining the stereoselectivity. The energy barrier corresponding to **TS2** of 48.2 kcal mol^{-1} in the gas phase decreases to 45.0 ($\varepsilon = 4.33$) and 42.8 kcal mol^{-1} ($\varepsilon = 37.0$) in solution. So the effect of solvent polarity in this case is a reduction in the rate-determining energy barrier of only 2.2 kcal mol^{-1} at the HF level. The kinetic data reported by Schaumann for the cycloaddition of di-*tert*-butylthioketene and 3,4-dihydroisoquinoline[3] at 120 °C imply a difference in activation energy of about 0.5 kcal mol^{-1} on passing from anisole to *N*,*N*-dimethylformamide. As already discussed in the unsubstituted system, the inclusion of correlation energy is expected to bring our theoretical results even closer to the experimental data. Thus our calculations model the behavior of this type of system reasonably well.

Summary

The most favorable mechanisms found for the cycloaddition of thioketene with formaldimine, both in the gas phase and in solution, are two- and three-step processes, which have in common a conrotatory electrocyclic closure to give the 2-thioazetidinone as the rate-determining step. According to our calculations, zwitterionic intermediates play a fundamental role in the mechanisms of this process. As expected, the electrostatic effect of solvent consists of a preferential stabilization of the zwitterionic structures $\mathbf{I_t}$, $\mathbf{I_g}$, and $\mathbf{TS_r}$. In agreement with experimental findings, our calculations show that the rate of this reaction is not very sensitive to solvent polarity. The effect of substituents is dominated by the torquoelectronic effect, so that, in contrast to previous interpretations, electronic effects are more important than steric effects.

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[1] W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, N.Y. **1990**.

[2] a) D. Bellus, B. Ernst, *Angew. Chem.* **1988**, *100*, 820–850; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 797–827; b) B. B. Snider, *Chem. Rev.* **1988**, *88*, 793–811; c) G. I. Georg, V. T. Ravikumar, in *The Organic Chemistry of β-Lactams* (Ed.: G. I. Georg), VCH, New York, **1993**.

[3] E. Schaumann, *Chem. Ber.* **1976**, *109*, 906–921.

[4] X. Creary, C. Zhu, *J. Am. Chem. Soc.* **1995**, *117*, 5859–5860.

[5] a) J. A. Sordo, J. González, T. L. Sordo, *J. Am. Chem. Soc.* **1992**, *114*, 6249–6251; b) X. Assfeld, J. A. Sordo, J. González, M. F. Ruiz-López, T. L. Sordo, *J. Mol. Struct. (Theochem)* **1993**, *287*, 193–199; c) X. Assfeld, M. F. Ruiz-López, J. González, R. López, J. A. Sordo, T. L. Sordo, *J. Comput. Chem.* **1994**, *15*, 479–487; d) R. López, T. L. Sordo, J. A. Sordo, J. González, *J. Org. Chem.* **1993**, *58*, 3263–3264; e) R. López, D. Suárez, M. F. Ruiz-López, J. González, J. A. Sordo, T. L. Sordo, *J. Chem. Soc. Chem. Commun.* **1995**, 1677–1678; f) R. López, M. F. Ruiz-López, D. Rinaldi, J. A. Sordo, T. L. Sordo, *J. Phys. Chem.* **1996**, *100*, 10600–10608.

[6] a) F. P. Cossío, J. M. Ugalde, X. López, B. Lecea, C. Palomo, *J. Am. Chem. Soc.* **1993**, *115*, 995–1004; b) F. P. Cossío, A. Arrieta, B. Lecea, J. M. Ugalde, *J. Am. Chem. Soc.* **1994**, *116*, 2085–2093; c) B. Lecea, I. Arrastia, A. Arrieta, G. Roa, X. López, M. I. Arriortua, J. M. Ugalde, F. P. Cossío, *J. Org. Chem.* **1996**, *61*, 3070–3079; d) D. C. Fang, X. Y. Fu, *Int. J. Quantum Chem.* **1996**, *57*, 1107–1114.

[7] M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Hill, M. W. Wong, J. B. Foresman, B. G. Johnson, B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. DeFrees, J. Baker, J. J. P. Stewart, J. A. Pople, *Gaussian 92*, Revision C; Gaussian, Pittsburgh PA, **1992**.

[8] Adapted by D. Rinaldi from D. Rinaldi, R. R. Pappalardo, Quantum Chemistry Program Exchange, Program no. 622, Indiana University, Bloomington, IN, **1992**.

[9] H. B. Schlegel, *J. Comput. Chem.* **1982**, *3*, 214–218.

[10] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648 – 5652; b) A. D. Becke, *Phys. Rev. A.* **1988**, *38*, 3098 – 3100; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B.* **1988**, *37*, 785 – 789.

[11] W. J. Hehre, L. Radom, J. A. Pople, P. von R. Schleyer, *Ab Initio Molecular Orbital Theory*, Wiley, New York, **1986**.

[12] D. A. McQuarrie, *Statistical Mechanics*, Harper & Row, New York, **1976**.

[13] a) J. L. Rivail, D. Rinaldi, M. F. Ruiz-López, in *Theoretical and Computational Model for Organic Chemistry* (*NATO ASI Series C, Vol. 339*) (Eds.: S. J. Formosinho, I. G. Csizmadia, L. Arnaut), Kluwer, Dordrecht, **1991**, pp. 79 – 92; b) V. Dillet, D. Rinaldi, J. G. Angyán, J. L. Rivail, *Chem. Phys. Lett.* **1993**, *202*, 18 – 22 ; c) V. Dillet, D. Rinaldi, J. L. Rivail, *J. Phys. Chem.* **1994,** *98*, 5034 – 5039.

[14] P. Claverie, in *Quantum Theory of Chemical Reactions*, *Vol. 3* (Eds.: R. Daudel, A. Pullman, L. Salem, A. Veillard), Reidel, Dordrecht, **1982**, pp. 151 – 175.

[15] S. Yamabe, T. Minato, Y. Osamura, *J. Chem. Soc. Chem Commun.* **1993**, 450 – 452.

[16] a) K. Fukui, *Acc. Chem. Res.* **1981**, *14*, 363 – 375; b) C. González, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523 – 5527.

[17] R. López, M. I. Menéndez, D. Suárez, T. L. Sordo, J. A. Sordo, *Comput. Phys. Commun.* **1993**, *76*, 235 – 249.

[18] W. R. Dolbier, H. Koronial, K. N. Houk, C. Sheu, *Acc. Chem. Res.* **1996**, 29, 471 – 477.

0947-6539/98/0402-0334 $ 17.50+.50/0