Solvent Effects on the Stereoselectivity of Ketene–Imine Cycloaddition Reactions

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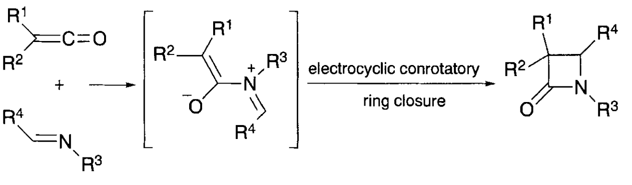
According to *ab initio* computations, the electrostatic solute–solvent interactions are predicted to be critical in the control of the stereoselectivity of the [2 + 2] ketene–imine cycloaddition reactions caused by the torquoelectronic effect.

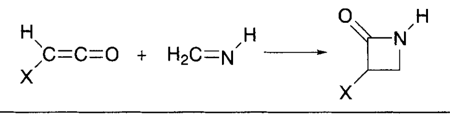
The [2 + 2] cycloaddition reaction of ketenes with imines, known as the Staudinger reaction, is a very efficient synthetic method for obtaining the biologically and clinically important β-lactams.[1] According to *ab initio* MP2/6-31G* calculations[2,3] this cycloaddition takes place in a two-step process through the formation of a zwitterionic intermediate which undergoes an electrocyclic conrotatory closure to give the final β-lactam (see Scheme 1). Gas-phase *ab initio* results show that the stereoselectivity of ring closure, which is predicted to be the rate-determining step of the reaction, is strongly influenced by the electronic nature of the substituents at position 3[4] according to the so-called torquoelectronic effect.[5] However, in order to make a comparison between *ab initio* results and condensed-phase experimental data, the effect of the solvent should be taken into account, especially in the case of polar transition structures.[3]

In the present work, *ab initio* MP2/6-31G* calculations have been carried out on gas-phase RHF/6-31G* geometries of the transition structures corresponding to the ring-closure step of the reaction of a series of substituted ketenes (see Table 1) with formaldimine by means of a general Self-Consistent-Reaction Field (SCRF) algorithm proposed for quantum chemical computations on solvated molecules.[6] For the –COMe substituent MP2/6-31G* computations have been performed on the fully optimized geometry of the solvated transition structure at the RHF/6-31G* level. The SCRF continuum model employed assumes a general cavity shape and a monocentric multipolar expansion of the electrostatic solvation energy, as described in ref. 6(*b*). Gas-phase free energy has been calculated by the standard procedures at 298.15 K and 1 atm (101 325 Pa). Free energy in solution has been obtained by adding to the gas-phase value the electrostatic free energy of solvation. Cavitation and dispersion contributions are expected to play a minor role on the stereoselectivity of the reaction and have been neglected.



Scheme 1

Table 1 Electrostatic free energies of solvation, $\Delta G^{\mathrm{elec}}_{\mathrm{solv}}$ (kcal mol^{-1}), for inward and outward stereoisomers of the substituted transition structures for the electrocyclic conrotatory ring closure of the zwitterionic intermediate in ketene–imine cycloaddition reactions, and differences in free energies (kcal mol^{-1}) between these isomers in a vacuum, ΔG^{vac}, and in solution, ΔG^{sol}

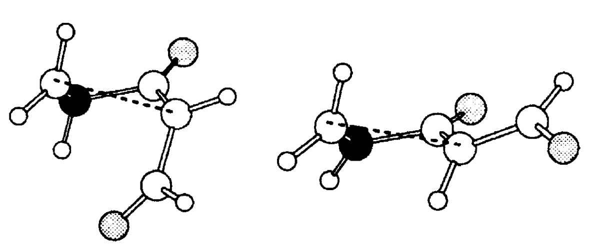


Group X	ΔG^{vac} (inw − out)	$\Delta G^{\mathrm{elec}}_{\mathrm{solv}}$ inw	$\Delta G^{\mathrm{elec}}_{\mathrm{solv}}$ out	ΔG^{solv} (inw − out)
OH	12.1	−6.0	−7.9	14.0
Me	9.2	−5.4	−5.2	9.0
CN	2.4	−7.4	−9.0	4.0
COMe				
conf. 1	−0.7	−4.7	−7.0	1.6
conf. 2	0.4	−7.9	−8.8	1.3
CHO				
conf. 1	−0.8	−4.8	−7.3	
conf. 2	−4.0	−8.2	−8.6	−1.7[a]
BH$_2$	−12.5	−5.9	−6.9	−11.5

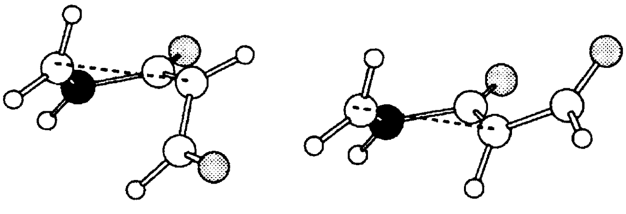
[a] Difference in free energy between the most stable inward (conf. 2) and the most stable outward (conf. 1) transition structures.

Table 1 collects the electrostatic ΔG of solvation of the inward and outward transition structures corresponding to the conrotatory closure of the zwitterionic intermediate, as well as the ΔG in a vacuum and in solution between the inward and outward stereoisomers. A relative permitivity of 8.93 has been used to simulate dichloromethane which is frequently used as a solvent in this kind of reactions. For the substituents –CHO and –COMe there are two different inward and outward structures differing in the carbonyl group conformation (see Fig. 1). As already reported,[4] in a vacuum a strong donor group (–OH) presents a preference for outward rotation whereas a strong acceptor group (–BH$_2$) presents a preference for inward rotation. Less strong acceptor groups present much less accentuated preferences for inward rotation (–CHO, –COMe, conformation 1), or even present decreasing preferences for outward rotation (–Me, –CN, –COMe, conformation 2).

In solution, the outward structures are more stabilized than the inward ones except for methylketene where the inward



Conformation 1 inward Conformation 1 outward



Conformation 2 inward Conformation 2 outward

Fig. 1 Conformations for the transition structure of ring closure in the reaction of formylketene with imine. Analogous structures have been found for the reaction of acetylketene with imine.

structure is slightly more stabilized than the outward one. This behaviour reflects the fact that in general the dipole moment of the outward transition structures is greater than that of the inward ones although in the case of methylketene both dipole moments are practically identical. This trend reinforces the gas-phase outward preferences but cannot invert the strongest gas-phase inward preferences. Thus for the reaction of hydroxyketene, methylketene, cyanoketene and borylketene with imine inward/outward preferences remain the same in solution as in the gas-phase.

The reactions between formylketene and acetylketene with imine present especially interesting features (see Fig. 2). In these two cases the inward transition structures of conformation 1 are only slightly more stable than the outward ones in gas-phase, and as the stabilization of the outward structures by the electrostatic interaction with the solvent is considerably higher, in solution the order of stability is reversed and the outward structures become the most stable ones. The outward transition structures of conformation 2 are 3.2 kcal mol^{-1} (1 cal ≈ 4.184 J) less stable (they present greater dipole moments) than those of conformation 1. The inward transition structure of conformation 2 for the reaction of formylketene has approximately the same free energy than that of conformation 1 whereas the inward transition structure of conformation 2 for the reaction of acetylketene is 0.4 kcal mol^{-1} less stable than the outward one because of the steric repulsion of the methyl group. Owing to the fact that the electrostatic solute–solvent interactions stabilize more conformation 2, with acetylketene the free energy levels of both conformations are interleaved in solution, and with formylketene the free energy levels corresponding to the inward and outward transition structures of conformation 1 are placed in solution between the free energy levels of the outward and inward structures of conformation 2 (see Fig. 2). Thus, the difference in free energy between the most stable inward and outward transition structures for the reaction of formylketene remains with the same sign in solution as in a vacuum. On the contrary, the difference in free energy between the most stable inward and outward transition structures for the reaction of acetylketene is reversed. This point has been confirmed by the analysis of the full optimized structures in solution which present a slightly later character compared with the gas-phase optimized ones.

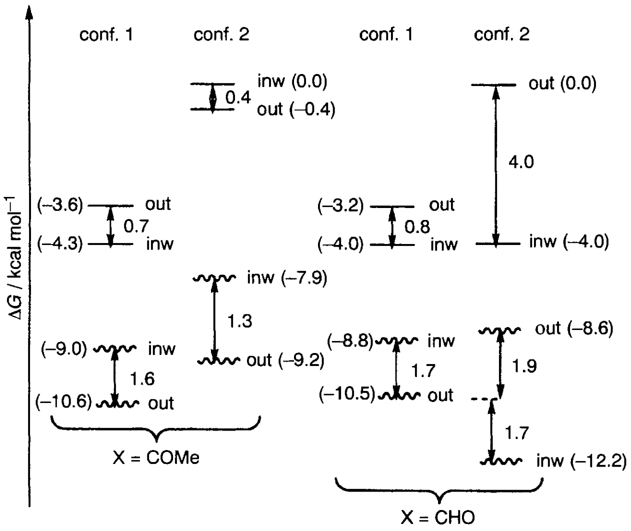


Fig. 2 Energy diagram of the transition structures for the ring closure in the reactions of formylketene and acetylketene with imine. Straight and wavy lines correspond to gas-phase and solution, respectively.

In summary, the electrostatic effect of the solvent is critical in the prediction of the stereoselectivity of the acetylketene + imine [2 + 2] cycloaddition reaction. Thus, from the present theoretical study it can be concluded that in those cases where the gas-phase inward-outward energy difference is small the effect of the solvent could be decisive.

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