Torquoelectronic Effect in the Control of the Stereoselectivity of Ketene–Imine Cycloaddition Reactions

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Ab initio calculations at the RHF/6-31G* and MP2/6-31G*//6-31G* theory levels show that the torquoelectronic effect is present in the ketene–imine cycloaddition reactions and is an important factor in the control of the reaction stereoselectivity.

The [2 + 2] cycloaddition reaction of ketenes with imines, usually known as the Staudinger reaction, constitutes a very efficient synthetic route to the biologically and clinically interesting β-lactams (Scheme I).[1]

The mechanism of this reaction has been a subject of controversy for several years, but some experimental evidence appears to support a stepwise process rather than a concerted one.[2] We have recently reported the results of ab initio calculations,[3] which indicate that the [2 + 2] cycloaddition of ketenes with imines takes place in a two-step process, through the formation of a zwitterionic intermediate, which undergoes a electrocyclic conrotatory closure to give the final β-lactam (Scheme I). At both the RHF/6-31G* and MP2/6-31G* theory levels the ring closure is predicted to be the rate-determining step of the reaction.[4]

The geometry of the transition structure corresponding to the conrotatory ring closure of the intermediate (Figure 1) is very close to those located for the electrocyclic ring opening of cyclobutenes.[5,6] In these cases, Houk and coworkers have discovered that the stereoselectivities of the thermal opening of 3-substituted cyclobutenes are strongly influenced by the electronic nature of the substituents at the carbons involved in the breaking bond.[5a] According to their calculations, *outward* rotations of the substituents in position 3 are favored by donors and *inward* rotations by powerful acceptors. This new type of stereoselectivity has been termed *torquoselectivity*.[5,6]

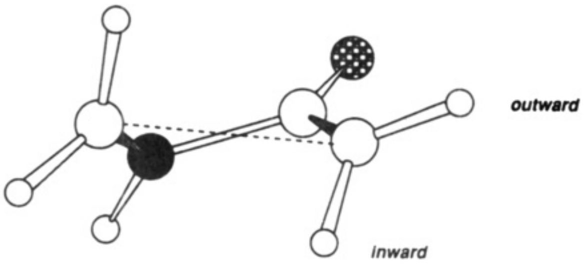
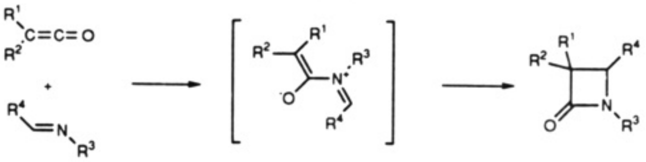


Figure 1. RHF/6-31G* optimized transition structure for the electrocyclic conrotatory ring closure of the zwitterionic intermediate in ketene–imine cycloaddition reactions (see ref 3).

Scheme I



In order to check if the above findings on torquoselectivity hold for the case of the [2 + 2] ketene–imine cycloadditions we have carried out ab initio calculations at the RHF/6-31G* and MP2/6-31G*//6-31G* theory levels,[7] investigating the effect of several substituents on the transition structure corresponding to the ring closure step of the reaction of substituted ketenes with formaldimine. The substituents studied are strong donors such as OH, F, and Cl, a mild donor such as the methyl group, and a strong acceptor such as the BH_2. The relative activation energies are indicated in Table I, and the corresponding transition structures located[8] are shown in Figure 2. As can be seen from these data, there is a strong preference for the outward rotation of the donor groups, while the powerful acceptor BH_2 prefers to rotate inward. These results are quite similar to the ones obtained in the case of the electrocyclic ring opening of the substituted cyclobutenes.[5,6]

As the transition structure corresponding to the conrotatory closure of the zwitterionic intermediate is the rate-determining step of the ketene–imine cycloaddition

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(1) For a review on the ketene–imine cycloaddition reaction see: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-lactams*; Georg, G. I., Ed.; VCH Publishers, Inc.: New York, 1993; p 295.

(2) Pacansky, J.; Chang, J. S.; Brown, D. W.; Schwarz, W. *J. Org. Chem.* **1982**, *47*, 2233.

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

(4) The presence of zwitterionic intermediates makes the influence of the solvent very important. Ab initio calculations including the electrostatic effect of the solvent show an important stabilization of the intermediate in condensed phases: Assfeld, X.; González, J.; López, R.; Ruiz-López, M. F.; Sordo, J. A.; Sordo, T. L., manuscript submitted for publication in *J. Comput. Chem.*

(5) (a) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (b) Houk, K. N.; Spellmeyer, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 3412. (c) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.

(6) (a) Houk, K. N. In *Strain and Its Implications in Organic Chemistry*; de Meijere, A., Blechert, S., Eds.; Kluwer Academic Publishers: New York, 1989; p 25. (b) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2127. (c) Buda, A. B.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 2266. (d) Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 6008. (e) Niwayama, S.; Houk, K. N. *Tetrahedron Lett.* **1993**, 1251.

(7) The calculations described here were performed with the *GAUSSIAN 88* series of programs: Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1988.

(8) The transition structures were located using Schlegel's algorithm[9] and characterized by calculation of the Hessian matrix.

(9) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 211.

0022-3263/93/1958-7036$04.00/0

Scheme II

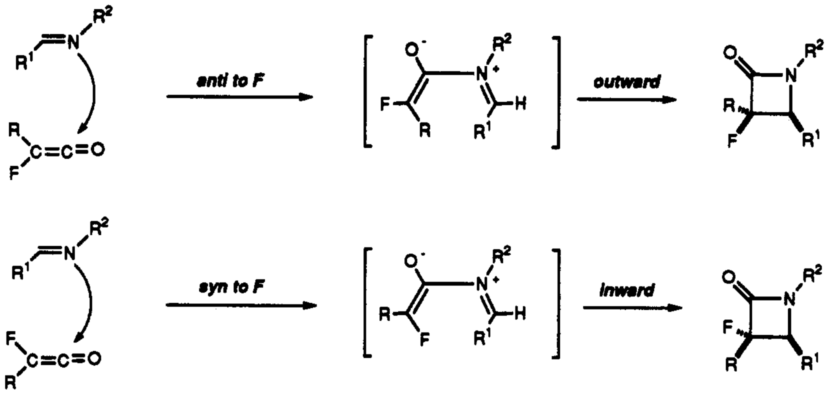
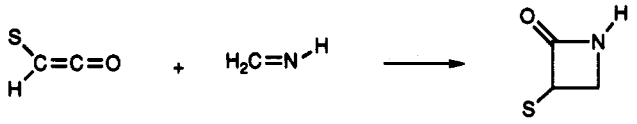


Table I. Influence of Ketene Substituents on the Stereochemistry of Ketene–Imine Cycloaddition



S	transitn struct[a]		E_a(inw − out)[b] RHF/6-31G*	E_a(inw − out)[b] MP2/6-31G*//6-31G*
OH	1 (inw)	2 (out)	10.1	12.3
Cl	3 (inw)	4 (out)	9.8	12.7
F	5 (inw)	6 (out)	9.6	11.2
CH_3	7 (inw)	8 (out)	8.8	8.5
H			0.0	0.0
BH_2	9 (inw)	10 (out)	−12.6	−14.9

[a] Transition structures numbered as in Figure 2. [b] Values in kcal mol^{-1}.

reaction,[3,4,10] the strong preference of donor or acceptor groups for outward or inward rotation, respectively, could be decisive in the control of the stereoselectivity of this reaction. Thus, for example, it has been reported recently that the reaction of imines with fluoroketenes is very stereoselective, this result not being related to the steric requirements of the other substituent on the α-carbon of ketene.[11] The only stereoisomer obtained corresponds to an addition of the imine *anti* to the fluorine of ketene (Scheme II). This experimental evidence is consistent with the fact that an *anti* addition leads to an intermediate which undergoes the conrotatory closure *via* a transition structure having the fluorine atom in the outward position. The alternative addition of the imine *syn* to the fluorine of the ketene would cause the fluorine atom to rotate inward in the closure of the intermediate, which is disfavored by about 11 kcal mol^{-1} at MP2/6-31G*//6-31G* level of theory, according to data in Table I. This effect appears to be operating also in the reactions of imines with several alkoxyketenes.[12]

The theoretical results presented in this paper clearly indicates that the torquoelectronic effect could play a relevant role in the control of the stereoselectivity of the [2 + 2] ketene–imine cycloaddition reactions.

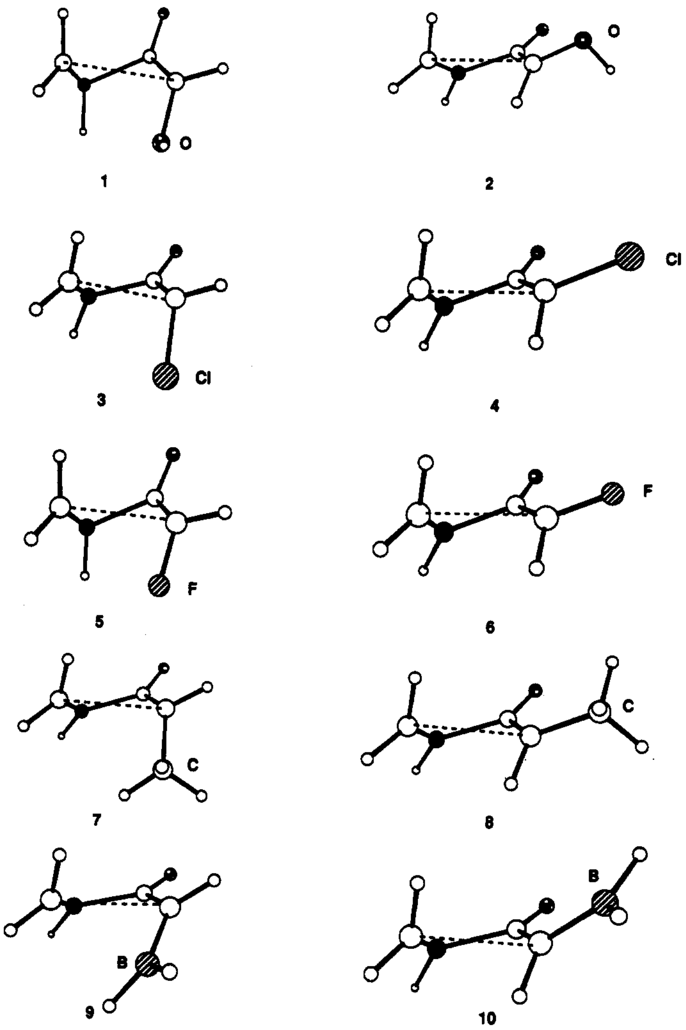


Figure 2. RHF/6-31G* optimized transition structures for the ring closure step in the cycloaddition reaction of substituted ketenes with formaldimine.

Acknowledgment. We are grateful to the Centro de Proceso de Datos de la Universidad de Oviedo for computer time.

Supplementary Material Available: Full geometries and energies of the transition structures 1–10 (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(10) The second step of the reaction, corresponding to the electrocyclic closure of the zwitterionic intermediate, is also the rate-determining step of the reactions involving substituted ketenes. Thus, RHF/6-31G* calculations in progress in our laboratory indicate that the first transition structure is always more stable, by about 16–20 kcal mol^{-1}, than the second transition structure, for the reactions of formaldimine with fluoro-, chloro-, and hydroxyketene.

(11) Araki, K.; Witchtowski, J. A.; Welch, J. T. *Tetrahedron Lett.* 1991, 5461.

(12) See, for example: Georg, G. I.; Ravikumar, V. T. in *The Organic Chemistry of β-lactams*; Georg, G. I., Ed.; VCH Publishers, Inc.: New York, 1993; p 303.