

# A Semiempirical Theoretical Study on the Formation of $\beta$ -Lactams from Ketenes and Imines

Fernando P. Cossio,<sup>\*,†</sup> Jesus M. Ugalde,<sup>\*,†</sup> Xavier Lopez,<sup>†</sup> Begoña Lecea,<sup>†</sup> and Claudio Palomo<sup>†</sup>

Contribution from the Departamento de Química Orgánica, Facultad de Química, Universidad del País Vasco, Ap. 1072, 20080 San Sebastián, Spain, and Kimika Fakultatea, Euskal Herriko Unibertsitatea, P.K. 1072, 20080 Donostia, Spain. Received July 23, 1992

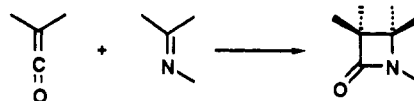
**Abstract:** Approximate self-consistent-field molecular orbital theory has been used to study the cyclization of ketenes and imines to  $\beta$ -lactams. In order to account for the effect of substituents, several substituted ketenes and imines have been carefully chosen. Calculations demonstrate that the reaction proceeds via a nonconcerted two-step mechanism, in good agreement with related experimental evidence. The first step involves formation of the  $N_1$ - $C_2$   $\beta$ -lactam bond, and the second step leads to ring closure through formation of the  $C_3$ - $C_4$  bond. The transition state associated with this latter step has significant biradical character, especially when there is a carbonyl group at the  $C_4$  position. Further, it has been found that the experimental stereoselectivity of the reaction is correctly predicted by the calculations. A general model of the stereochemical trends of the Staudinger reaction is proposed on the basis of the possible different approaches of imines to ketenes as well as the perturbational effects induced by the substituents at the  $C_3$  and  $C_4$  positions of the  $\beta$ -lactam ring.

## Introduction

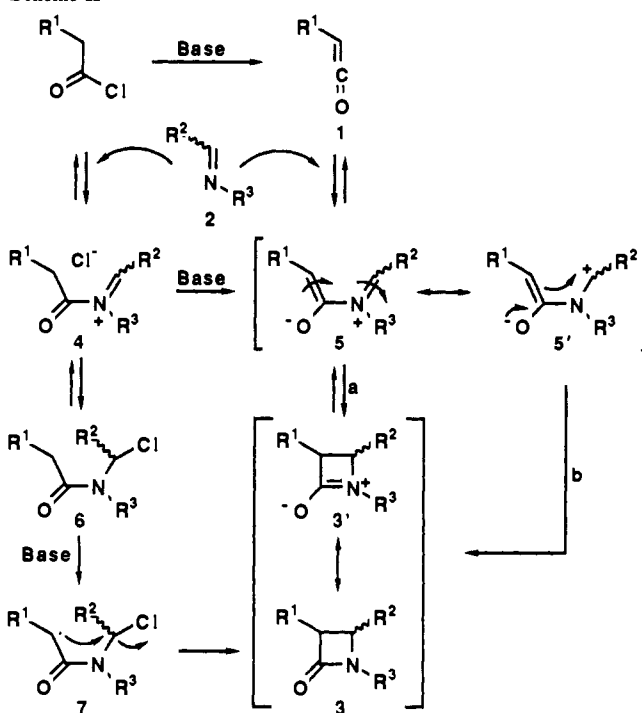
The reaction of ketenes with imines to form 2-azetidiones (Scheme I), known as the Staudinger reaction (SR),<sup>1</sup> and its variants<sup>2,3</sup> are some of the most useful procedures both for constructing the  $\beta$ -lactam skeleton<sup>3</sup> present in the different families of  $\beta$ -lactam antibiotics<sup>4</sup> and also for synthesizing compounds that use  $\beta$ -lactams as starting materials.<sup>5</sup>

At least a concerted one-step pericyclic and a two-step nonconcerted mechanism can be envisaged for the cyclization reaction between ketenes and imines.<sup>6</sup> Early proposals of the mechanism of the SR focused on the theory of conservation of orbital symmetry. Thus, within this theory, [2 + 2] cycloadditions are allowed when the interaction between the two partners is in a [ $\pi_2$ ,  $\pi_2$ ] mode.<sup>7</sup> In the case of ketenes, orbital symmetry and steric considerations<sup>8</sup> favor supraantara geometries for the transition state. This type of mechanism has been suggested for cases in which the nucleophilicity of the nitrogen lone pair of the imine is strongly diminished by the inductive electron-withdrawing effect of the substituents.<sup>6</sup> However, recent research has pointed out that related cycloaddition reactions, namely those of alkenes with ketenes or allenes,<sup>9,10</sup> have been satisfactorily explained in terms of a concerted [ $\pi_2$ ,  $\pi_2$ ] mechanism. However, this result has not been extended to the case of the SR, probably because of the simultaneous presence of a carbon-nitrogen double bond and an iminic nitrogen lone pair. In this sense, it is widely assumed that the cyclization of ketenes and imines proceeds via formation of a C-N bond at the early stages of the reaction. Nevertheless, there exists a great deal of controversy concerning not only the mechanism of the SR itself but also that of its variants, in which more accessible synthetic equivalents of ketenes, such as acyl halides<sup>2</sup> or activated substituted acetic acids,<sup>11</sup> are used. In fact, it has been suggested that more than one mechanism could be operating simultaneously.<sup>3a,6</sup> Scheme II outlines the main reaction mechanisms that have been proposed in the literature to rationalize the experimental findings. Thus, the reaction between acyl chlorides and imines is assumed to proceed through in situ formation of a ketene (1), followed by interaction with imine 2 to form the zwitterion 5, which undergoes an electrocyclic conrotatory ring closure to the  $\beta$ -lactam (3  $\leftrightarrow$  3') ring. This mechanism has proved very useful in accounting for the observed stereochemical course<sup>12</sup> of the SR. In particular, Hegedus et al. have recently reported<sup>13</sup> an excellent discussion of the stereochemical consequences of this type of mechanism. Another possible reaction pathway<sup>14</sup> consists of direct interaction between the acyl chloride

## Scheme I



## Scheme II



and the imine to give adduct 4, which undergoes nucleophilic attack by the chloride anion to afford the chloroamide 6. (This

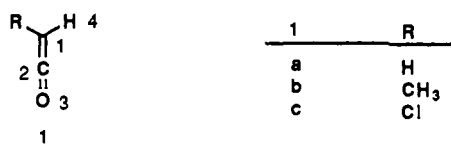
(1) (a) Staudinger, M. *Liebigs Ann. Chem.* **1907**, 356, 51. (b) For a review on chiral control of the Staudinger reaction, see: Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure Appl. Chem.* **1987**, 59, 485. (c) Thomas, R. C. In *Recent Progress in The Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1988; p 533. (d) Van der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, 47, 7503.

(2) For the acid chloride-imine approach, see, for example: (a) Sheehan, J. C.; Ryan, J. J. *J. Am. Chem. Soc.* **1951**, 73, 1204. (b) Manhas, M. S.; Chib, J. S.; Chiang, Y. H.; Bose, A. K. *Tetrahedron* **1969**, 25, 4421. (c) Evans, D. A.; Sjögren, E. B. *Tetrahedron Lett.* **1985**, 26, 3783 and 3787.

<sup>\*</sup> Departamento de Química Orgánica.

<sup>†</sup> Kimika Fakultatea.

Chart I



intermediate, which is also accessible from zwitterion **5** by the addition of nucleophiles, has been isolated.<sup>15</sup>) Finally, abstraction of a proton by 1 equiv of base (usually triethylamine) followed by an enolate nucleophilic displacement forms the  $\beta$ -lactam ring **3**. This reaction mechanism has been criticized recently by Lynch et al.,<sup>16</sup> who found that in the acid chloride-imine reaction the ketene is formed prior to the cycloaddition stages. This result suggests that the SR proceeds most likely through the  $1 + 2 \rightarrow 5 \rightarrow 3$  sequence of Scheme II. On the other hand, experimental evidence suggests that structure **5** is an intermediate prior to the cyclization process and has been the subject of a recent discussion by Brady and Gu.<sup>17</sup> These authors claim that if the resonance structure **5'** makes a significant contribution to the structure of intermediate **5**, then cyclization could be occurring via pathway **b** as shown in Scheme II.

Very little theoretical work has been published on the nature of the SR.<sup>1b,18</sup> Boyd et al.<sup>1b</sup> have reported a MNDO calculation

Chart II



	2	R <sup>1</sup>	R <sup>2</sup>
a		H	H
b		CH <sub>3</sub>	H
c		CH=CH <sub>2</sub>	H
d		C <sub>6</sub> H <sub>5</sub>	H
e		CHO	H
f		CH <sub>3</sub>	CH <sub>3</sub>
g		CH=CH <sub>2</sub>	CH <sub>3</sub>
h		C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
i		CHO	CH <sub>3</sub>

Chart III



	3	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
a		H	H	H
b		H	CH <sub>3</sub>	H
c		H	CH=CH <sub>2</sub>	H
d		H	C <sub>6</sub> H <sub>5</sub>	H
e		H	CHO	H
f		H	CH <sub>3</sub>	CH <sub>3</sub>
g		H	CH=CH <sub>2</sub>	CH <sub>3</sub>
h		H	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
i		H	CHO	CH <sub>3</sub>
j		Cl	CH=CH <sub>2</sub>	CH <sub>3</sub>
k		Cl	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
l		Cl	CHO	CH <sub>3</sub>
m		CH <sub>3</sub>	CH=CH <sub>2</sub>	CH <sub>3</sub>
n		CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>
o		CH <sub>3</sub>	CHO	CH <sub>3</sub>

(3) For reviews on the synthesis of  $\beta$ -lactams, see: (a) Mukerjee, A. K.; Srivastava, R. C. *Synthesis* 1973, 32. (b) Bose, A. K.; Manhas, M. S. *Lect. Heterocycl. Chem.* 1976, 3, 43. (c) Isaaks, N. S. *Chem. Soc. Rev.* 1976, 5, 181. (d) Mukerjee, A. K.; Singh, A. K. *Tetrahedron* 1978, 34, 1731. (e) Ghosez, L.; Marchand-Brynaert, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 85.

(4) For reviews on  $\beta$ -lactam antibiotics, see: *Chemistry and Biology of  $\beta$ -Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1-3.

(5) For review, see: (a) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* 1976, 5, 669. (b) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* 1988, 27, 1755.

(6) Holden, K. G. In *Total Synthesis of Penicillins Cefalosporins, and Their Nuclear Analogs*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, pp 99-164.

(7) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970.

(8) (a) Pearson, R. G. *Symmetry Rules for Chemical Reactions. Orbital Topology and Elementary Processes*; Wiley: New York, 1976; p 360. (b) Houk, K. N.; Strozier, R. W.; Hall, J. A. *Tetrahedron Lett.* 1974, 897.

(9) Pasto, D. J. *J. Am. Chem. Soc.* 1979, 101, 37.

(10) Valenti, E.; Pericás, M. A.; Moyano, A. *J. Org. Chem.* 1990, 55, 3582.

(11) (a) Aizpurua, J. M.; Ganboa, I.; Cossio, F. P.; González, A.; Arrieta, A.; Palomo, C. *Tetrahedron Lett.* 1984, 25, 3905. (b) Arrieta, A.; Cossio, F. P.; Palomo, C. *Tetrahedron* 1984, 41, 1703. (c) Arrieta, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* 1984, 25, 3365. (d) Cossio, F. P.; Ganboa, I.; Palomo, C. *Tetrahedron Lett.* 1985, 26, 3041. (e) Cossio, F. P.; Ganboa, I.; Garcia, J. M.; Lecea, B.; Palomo, C. *Tetrahedron Lett.* 1987, 28, 1945. (f) Bose, A. K.; Manhas, M. S.; Van der Veen, J. M.; Amin, S. G.; Fernández, I. F.; Gala, K.; Gruska, R.; Kapur, J. C.; Khajavi, M. S.; Kreder, J.; Mukkavilli, L.; Ram, B.; Sugiura, M.; Vincent, J. E. *Tetrahedron* 1981, 37, 2321. (g) Manhas, M. S.; Bose, A. K.; Khajavi, M. S. *Synthesis* 1981, 209. (h) Sharma, S. D.; Gupta, P. K. *Tetrahedron Lett.* 1978, 4578. (i) Shridar, S. D.; Ram, B.; Narayana, V. L. *Synthesis* 1982, 63. (j) Arrieta, A.; Lecea, B.; Palomo, C. *J. Chem. Soc., Perkin Trans. I* 1987, 845.

(12) (a) Moore, H. W.; Hughes, G.; Srinivasachar, F.; Fernández, M.; Nguyen, N. V.; Schoon, D.; Tranne, A. *J. Org. Chem.* 1985, 50, 4231. (b) Hubschwerlen, C.; Schmidt, G. *Helv. Chim. Acta* 1983, 66, 2206. (c) Aizpurua, J. M.; Cossio, F. P.; Lecea, B.; Palomo, C. *Tetrahedron Lett.* 1986, 27, 4359. (d) Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* 1988, 29, 5065. (e) Alcaide, B.; Dominguez, G.; Plumet, J.; Sierra, M. A. *Heterocycles* 1988, 27, 1317.

(13) Hegedus, L. S.; Montgometry, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* 1991, 113, 5784.

(14) (a) Just, G.; Hakimelahi, G. H.; Ugolini, A.; Zamboni, R. *Synth. Commun.* 1979, 9, 113. (b) Just, G.; Ugolini, A.; Zamboni, R. *Synth. Commun.* 1979, 9, 117. (c) Doyle, T. W.; Belleau, B.; Lum, B.-Y.; Ferrari, C. F.; Cunningham, M. P. *Can. J. Chem.* 1977, 55, 468. (d) Bose, A. K.; Chiang, Y. H.; Manhas, M. S. *Tetrahedron Lett.* 1972, 4091.

(15) (a) Duran, F.; Ghosez, L. *Tetrahedron Lett.* 1970, 245. (b) Nelson, D. A. *J. Org. Chem.* 1972, 37, 1447; (c) Decazes, J. M.; Luche, J. L.; Kagan, H. B. *Tetrahedron Lett.* 1972, 3633. (d) Bellus, D. *Helv. Chim. Acta* 1975, 58, 2509.

(16) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* 1989, 54, 3792.

(17) Brady, W. T.; Gu, Y. Q. *J. Org. Chem.* 1989, 54, 2838.

concerning the geometry of the zwitterionic intermediate and the reaction product in the interaction between methylketene and (Z)-N-methylmethanimine. Their principal conclusion is that the interaction between the ketene and the imine can occur in a non-coplanar fashion, and therefore the formation of the C<sub>3</sub>-C<sub>4</sub> bond via a conrotatory cyclization implies not only torsion of the  $\pi$ -systems of both reactants but also rotation around the N<sub>1</sub>-C<sub>2</sub> bond to reach its final eclipsed arrangement. This prediction is corroborated, and, in addition, details of the structure and energy of the possible transition states involved in such a process are determined in the present work.

In the light of the above comments and in connection with our interest in  $\beta$ -lactam chemistry, the aim of this work was to clarify, from a theoretical standpoint, the qualitative arguments discussed above and hence improve our knowledge of the behavior of imines and ketenes in the formation of  $\beta$ -lactams. Thus, the goals of our research were 3-fold: first, to carry out a study of the reaction between ketene and methanimine to yield 2-azetidinone, the simplest  $\beta$ -lactam skeleton; second, to evaluate the imine effect by studying the reaction of several properly selected imines with ketene to give 4-substituted  $\beta$ -lactams; and third, to discuss and predict the general stereoselectivity trends of the SR between

(18) Boyd, D. B. *Computer-Assisted Molecular Design Studies of  $\beta$ -Lactam Antibiotics*. In *Frontiers on Antibiotic Research*; Umezawa, H., Ed. Academic Press; Tokyo, 1987; pp 339-356.

unsymmetrically substituted ketenes and aldimines. This latter aspect should add valuable information on the utility of this reaction for the synthesis of both cis and trans 3,4-disubstituted  $\beta$ -lactams.

## Methods

The semiempirical SCF-MO MNDO<sup>19</sup> and AM1<sup>20</sup> methods (mainly the latter) have been used in this work. Calculations were carried out with the standard parameters<sup>20,21</sup> using locally modified versions<sup>22</sup> of the MOPAC packages<sup>23</sup> which include the AM1 Hamiltonian.

Equilibrium geometries for reactants and products were determined by minimization of the energy with respect to all geometrical parameters using the DFP algorithm.<sup>24</sup> The ketenes, imines, and  $\beta$ -lactams studied are depicted in Charts I-III. The potential energy surface corresponding to the interaction between ketene and methanimine (vide infra) was calculated by optimizing all variables except the  $N_1-C_2$  and  $C_1-C_4$  distances, which were kept fixed at selected values. This allowed identification of approximate stationary structures, which were further optimized with either NLLSQ<sup>25</sup> and/or POWELL<sup>26</sup> algorithms. All stationary points were refined by minimization of the gradient norm of the energy<sup>27</sup> and characterized by harmonic vibrational frequency analysis. Inspection of the number of negative eigenvalues occurring in their corresponding force constant matrices accordingly led to classification<sup>27</sup> of the stationary structures. The other stationary points were obtained by pertinent substitution on other previously located structures and further optimization with the NLLSQ or POWELL algorithms.

All ab initio results presented in this work were obtained using the GAUSSIAN 90 series of programs.<sup>28</sup> Throughout this paper the 6-31G\* basis set has been used. Geometry optimizations and subsequent frequency analyses were carried out with the RHF and the multiconfigurational SCF (CASSCF) approximations. We found it important to use at least a minimal active space including two electrons and two orbitals. This level of theory, which is customarily denoted as two-configuration SCF (TCSCF), is the minimum treatment needed for a proper description of singlet biradicaloids. Also, it was long ago recognized<sup>29</sup> that TCSCF is the simplest wave function permitting a qualitative comparison of singlet and triplet energy levels. The importance of the antibonding orbitals will be assessed by means of the natural orbital occupation numbers. For triplet states, both orbitals are singly occupied, but for the TCSCF singlet the occupation numbers  $N(\Phi)$  and  $N(\Phi^*)$ , which sum to exactly 2, are, in general, different and provide a direct quantitative measure of how close the wave function is to complete biradical character, i.e.,  $N(\Phi) = N(\Phi^*) = 1$ . The reasons for choosing these particular options are discussed in the text.

All the calculations included in our study refer to the gas phase; therefore, the solvent effect on the SR has not been investigated.

## Results and Discussion

**Reaction between Ketene and Methanimine.** The first process studied was the reaction between ketene (**1a**) and methanimine (**2a**) to give azetidin-2-one (**3a**), in order to evaluate the different types of interactions between the simplest partners. Inspection of the results corresponding to diverse computational levels shows that calculated optimized geometries of ketene (**1a**) and metha-

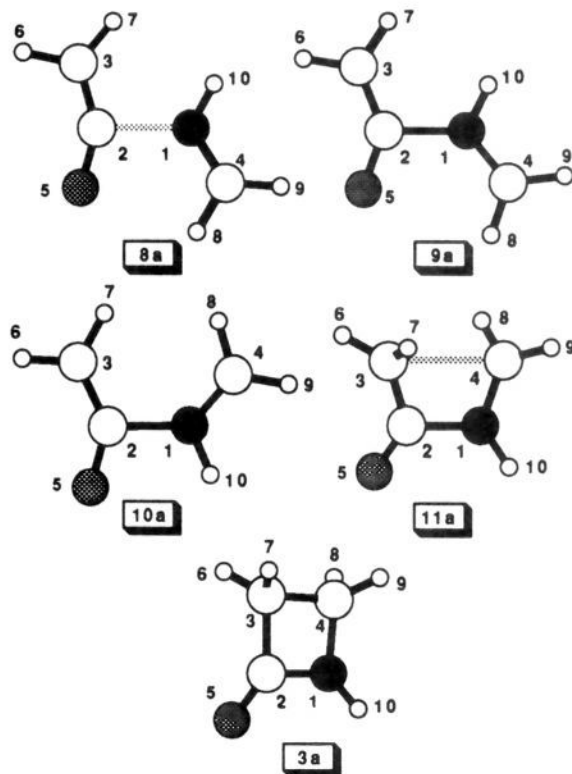


Figure 1. Stationary points found in the Staudinger reaction between ketene (**1a**) and methanimine (**2a**) to give azetidin-2-one (**3a**).

nimine (**2a**) using both MNDO and AM1 semiempirical MO methods compare well with those obtained by ab initio calculations<sup>30a,31</sup> with basis sets including polarization functions. Table III of the supplementary material reveals that standard MNDO and AM1 SCF calculations lead to closer agreement with experimental X-ray data<sup>32</sup> than minimal basis set ab initio calculations<sup>33</sup> for the 2-azetidinone (**3a**) reaction product. The largest disagreement between the aforementioned X-ray data and either MNDO or AM1 (particularly the former) results is for the  $N_1-C_2$  bond length. However, as has been pointed out,<sup>34</sup> the C-N amide bond length is considerably shorter in solid amides due to hydrogen-bond-type interactions. This effect is probably responsible for at least part of the 0.072 and 0.062 Å shrink of the solid-phase amide bond length with respect to MNDO and AM1 predictions, respectively. However, there is a systematic error in this bond distance. For example, Frau et al.<sup>35</sup> have reported that in bicyclic  $\beta$ -lactam antibiotics the AM1 method predicts the geometry of the system quite well, except for the  $N_1-C_2$  bond length and the pyramidal character of the  $\beta$ -lactam nitrogen, which are both overestimated. Therefore, since monocyclic  $\beta$ -lactams are reported to be almost planar, we have recalculated the structures and the energies of  $\beta$ -lactams **3a-o** using the MMOK option. Results are given in Table III of the supplementary material. Slight discrepancies, mainly for the dihedral angle, have been found only for N-unsubstituted  $\beta$ -lactams. In the remaining cases the effect of including the torsion potential was negligible. In summary,

(19) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

(20) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(21) (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907. (b) Dewar, M. J. S.; Zoebisch, E. G. *J. Mol. Struct. (THEOCHEM)* **1988**, *180*, 1.

(22) Olivella, S. *QCPE Bull.* **1984**, *9*, 10. Extended by Olivella, S.; Bofill, J. M., **1990**.

(23) (a) Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 101. (b) *QCPE* # 455. Indiana University, Bloomington, Indiana, USA.

(24) (a) Fletcher, R.; Powell, M. J. D. *Comput. J.* **1963**, *6*, 163. (b) Davidson, W. C. *Comput. J.* **1968**, *11*, 406.

(25) Bartels, R. H. Report CNA-44; University of Texas Center for Numerical Analysis.

(26) Powell, M. J. D. In *Numerical Methods for Nonlinear Algebraic Equations*; Rabinowitz, P., Ed.; Gordon Breach: New York, 1970.

(27) McIver, J. W., Jr.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

(28) Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; DeFrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. *Gaussian 90, Revision 1*; Gaussian, Inc., Pittsburgh, PA, 1990.

(29) Bender, C. F.; Schaefer, H. F., III; Franceschetti, D. R.; Allen, L. C. *J. Am. Chem. Soc.* **1972**, *94*, 6888.

(30) (a) Tanaka, K.; Yoshimine, M. *J. Am. Chem. Soc.* **1980**, *102*, 7655.

(b) Cox, J. O.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: New York, NY, 1970.

(31) (a) Riggs, N. V.; Radom, L. *Int. J. Quantum Chem.* **1987**, *37*, 393. (b) DeFrees, D. J.; Raghavachari, K.; Schlegel, H. B.; Pople, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 5576.

(32) Yang, B. Q.; Seiler, P.; Dunitz, J. D. *Acta Crystallogr., Sect. C* **1987**, *43*, 567.

(33) Sedano, E.; Ugalde, J. M.; Cossio, F. P.; Palomo, C. *J. Mol. Struct. (THEOCHEM)* **1988**, *166*, 481.

(34) Chakrabarti, P.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *65*, 1555.

(35) (a) Frau, J.; Coll, M.; Donoso, J.; Muñoz, F.; Garcia-Blanco, F. *J. Mol. Struct. (THEOCHEM)* **1991**, *231*, 109. (b) Frau, J.; Donoso, J.; Muñoz, F.; Garcia-Blanco, F. *Ibid.* **1991**, *251*, 205.

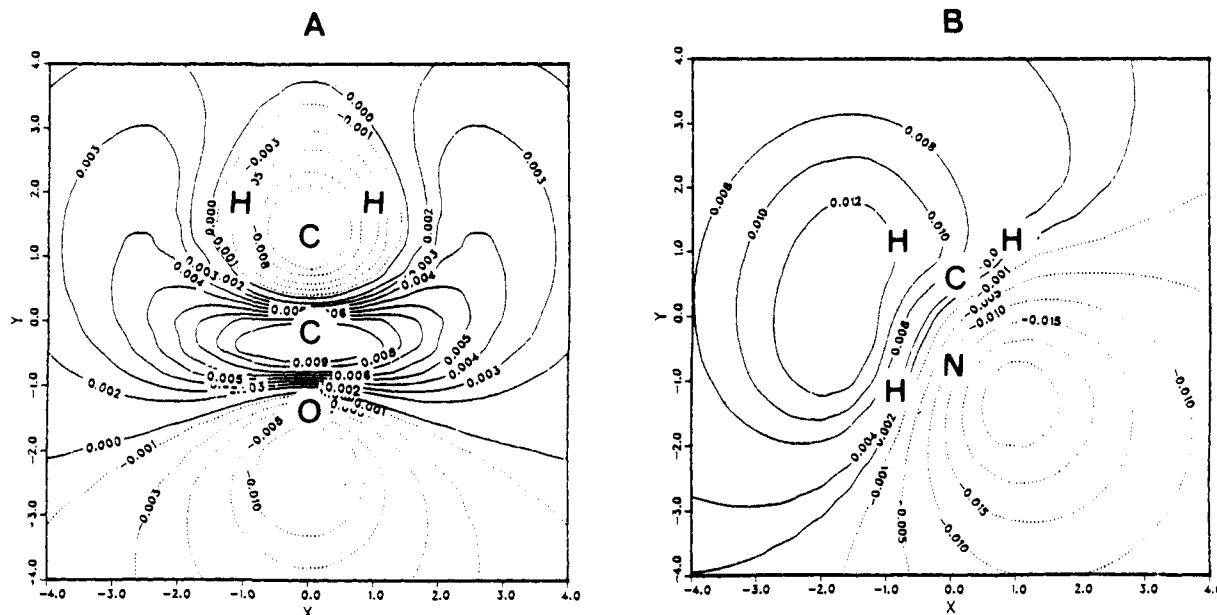


Figure 2. STO-5G Electrostatic potential of (A) ketene (**1a**) and (B) methanimine (**2a**), calculated at 1.75 Å above the molecular plane. Solid and dotted contours represent positive and negative potentials, respectively. All values are given in hartrees.

our MNDO and AM1 results for the ground-state structures of the reactants and products have been shown to compare reasonably well with experimental and high-level split valence ab initio calculations. We shall comment on the behavior of transition-state structures later.

The stationary structures found in the reaction between **1a** and **2a** are also shown in Figure 1, and some of their geometric and electronic structural features are reported in Table I and in Table IV of the supplementary material. Inspection of the AM1 potential energy surface reveals a two-step nonconcerted mechanism.<sup>36</sup> The first step consists of formation of the  $N_1-C_2$  bond via transition state **8a** (see Figure 1), formed by nucleophilic attack of methanimine's nitrogen lone pair on the central carbon atom of the ketene. It is interesting to note that in **8a** there is a null bond index between  $C_3$  and  $C_4$ , indicating that formation of the  $N_1-C_2$  and  $C_3-C_4$  bonds occurs in a completely asynchronous manner. The AM1 and MNDO bond distances for this first transition state are 1.856 and 1.857 Å, respectively. Inspection of the electrostatic potentials located at 1.75 Å above the molecular plane of ketene and methanimine (Figure 2) clearly indicates that there exists a strongly electrophilic center at the central carbon of ketene (**1a**) able to interact positively with the nucleophilic nitrogen of methanimine (**2a**). Therefore, the electrostatic interaction between methanimine's nucleophilic nitrogen (mainly due to its lone pair) and the electrophilic central atom of ketene appears to be the dominant driving force in the initial stages of the SR. Inspection of the frontier orbitals of **1a** and **2a** (Figure 3) also suggests that nucleophilic attack occurs through the molecular planes of both partners and is not orthogonal to the molecular plane of **2a**. This effect, due to the presence of the iminic nitrogen lone pair, is responsible for the mechanistic differences of the Staudinger reaction with respect to cycloaddition between ketenes and olefins.<sup>10,37</sup>

A long-range interaction adduct (**9a**) with a calculated  $N_1-C_2$  distance of 1.603 Å with MNDO and 1.536 Å with the AM1 method has also been found. This adduct is formed through the transition state **8a** with activation barriers of 18.0 and 16.5

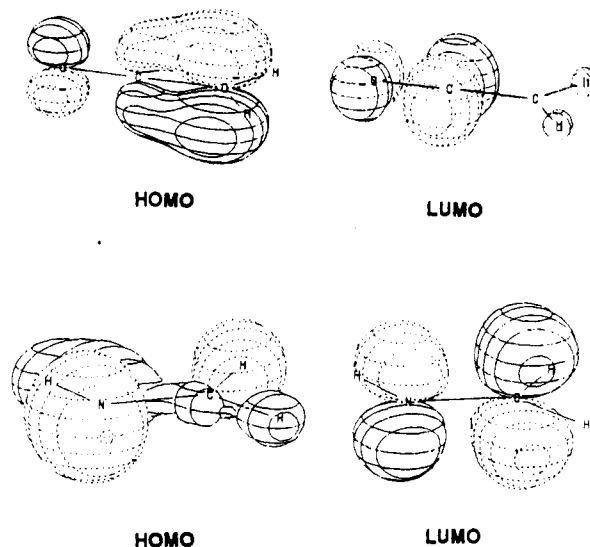


Figure 3. PSI/77 plot of the orthogonalized frontier canonical orbitals corresponding to ketene (**1a**) and methanimine (**2a**).

kcal/mol (MNDO and AM1, respectively). This intermediate has been postulated by many authors<sup>12</sup> in order to account for the formation of  $\beta$ -lactams in the SR (see Scheme II) and, in a favorable case,<sup>38</sup> has been detected and characterized by IR spectroscopy. It is found that the zwitterionic intermediate **9a** is located on a *plateau* of the potential energy surface corresponding to  $N_1-C_2$  distances ranging from approximately 1.6 to 1.5 Å and  $C_3-C_4$  distances between 3.7 and 3.5 Å. This feature allows significant variations of the geometry at low energy cost. The increase of the  $O_5-C_2-N_1$  angle from 104.6° in **8a** to 111.2° in **9a** (AM1 results) may be interpreted in terms of a partial loss of the sp hybridization character of the ketene central carbon. However, the MNDO output of the  $O_5-C_2-N_1$  angle as 109.2° in **9a** reveals that in the corresponding Hamiltonian a higher sp character is retained until the final stages of the  $N_1-C_2$  bond formation process. In fact, the MNDO/RHF results lead to slightly earlier stationary points with respect to the AM1/RHF ones. The AM1 bond index between  $N_1$  and  $C_2$  is still 0.47, whereas its final value in **3a** is 1.02. The bond order between  $C_3$

(36) A stationary point was found in the potential energy surface which corresponded to a possible one-step concerted mechanism ( $d_{12} \approx d_{34}$ ). However, the harmonic analysis revealed that it was not a transition state (more than one imaginary eigenvalue in the force matrix). In fact, we have not been able to find a true transition state corresponding to [ $\pi_2s + \pi_2a$ ] or [ $\pi_2s + (\pi_2s + \pi_2s)$ ] concerted mechanisms.

(37) (a) Burke, L. A. *J. Org. Chem.* **1985**, *50*, 3149. (b) Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 1754. (c) Bernardi, F.; Bottoni, A.; Robb, M. A.; Venturini, A. *J. Am. Chem. Soc.* **1990**, *112*, 2106.

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

Table I. Salient Properties<sup>a</sup> of the Fully Optimized Stationary Structures 8-11a

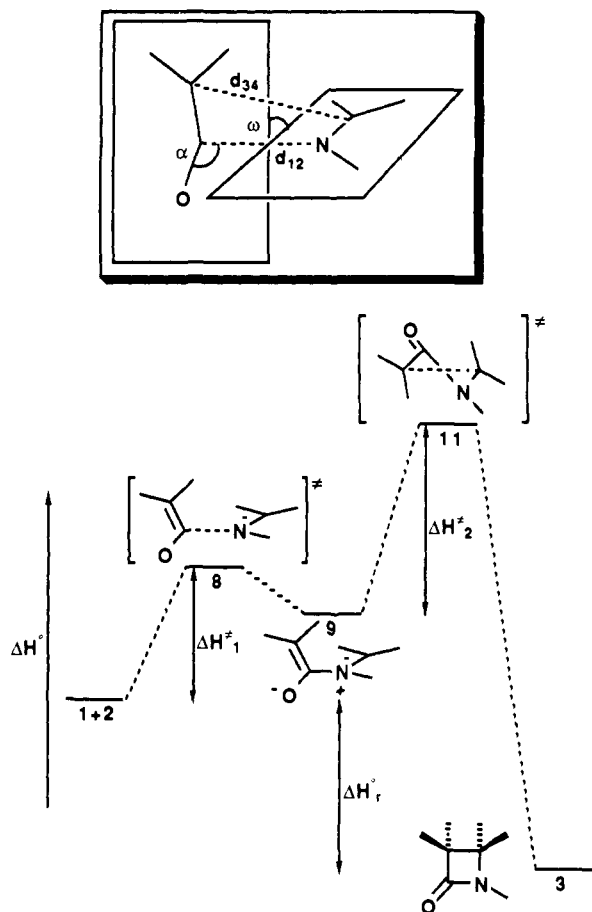
	8a			9a			10a			11a		
	MNDO RHF	AM1 RHF	TCSCF/6-31G*	MNDO RHF	AM1 RHF	TCSCF/6-31G*	MNDO RHF	AM1 RHF	TCSCF/6-31G*	AM1 RHF	3X3CI-HE	TCSCF/6-31G*
$\Delta H_f$ (kcal/mol)	30.6	29.3	24.9	-245.73387	-245.75465	-245.74204	30.8	25.8	25.4	20.0	84.1i	-245.69003
energy (au)	483.0i	482.8i					93.0i		534.5i		692.1i	195.1i
$\nu$ (cm <sup>-1</sup> ) <sup>c</sup>												
	Bond Distances (Å)											
N <sub>1</sub> -C <sub>4</sub>	1.273	1.273	1.287	1.254	1.256	1.256	1.300	1.285	1.342	1.361	1.361	1.391
N <sub>1</sub> -C <sub>2</sub>	1.857	1.856	1.536	1.580	1.548	1.548	1.609	1.528	1.453	1.408	1.400	1.365
C <sub>2</sub> -C <sub>3</sub>	1.333	1.333	1.359	1.342	1.356	1.356	1.363	1.360	1.432	1.468	1.468	1.470
C <sub>2</sub> -O <sub>5</sub>	1.221	1.222	1.255	1.214	1.224	1.224	1.229	1.255	1.239	1.240	1.240	1.200
C <sub>3</sub> -C <sub>4</sub>	3.935	3.734	3.625	3.542	3.543	3.543	3.068	2.957	2.331	2.885	2.885	2.701
N <sub>1</sub> -H <sub>10</sub>	0.995	0.995	1.003	1.002	1.001	1.001	1.015	1.012	0.991	0.987	0.999	0.999
	Bond Angles (deg)											
C <sub>2</sub> -N <sub>1</sub> -C <sub>4</sub>	121.6	121.6	122.9	120.0	120.3	120.3	132.0	128.3	109.1	107.6	124.1	109.4
N <sub>1</sub> -C <sub>2</sub> -O <sub>5</sub>	104.6	104.6	111.2	110.8	111.6	111.6	106.4	107.6	121.3	125.6	118.2	122.5
C <sub>2</sub> -N <sub>1</sub> -H <sub>10</sub>	116.9	116.9	116.1	120.0	119.8	119.8	113.0	120.5	124.9	124.9	116.2	123.5
H <sub>6</sub> -C <sub>3</sub> -C <sub>1</sub>	117.7	118.0	119.5	119.2	119.3	119.3	126.0	125.5	118.3	118.4	118.2	118.6
H <sub>8</sub> -C <sub>4</sub> -N <sub>1</sub>	125.2	125.7	122.8	116.6	116.5	116.5	122.6	122.4	121.7	119.3	120.2	119.2
	Dihedral Angles (deg)											
C <sub>4</sub> -N <sub>1</sub> -C <sub>2</sub> -C <sub>3</sub>	178.0	179.9	178.3	179.9	180.0	180.0	0.0	0.0	17.8	16.6	7.1	21.8
H <sub>6</sub> -C <sub>3</sub> -C <sub>2</sub> -N <sub>1</sub>	179.8	180.0	179.9	180.0	180.0	180.0	180.0	180.0	148.2	102.6	134.7	170.0
H <sub>8</sub> -C <sub>4</sub> -N <sub>1</sub> -C <sub>2</sub>	0.2	0.1	0.2	0.0	0.0	0.0	0.0	0.0	45.8	100.7	5.5	48.3

<sup>a</sup>For the numbering of the atoms, see Figure 1. <sup>b</sup> $\langle S^2 \rangle = 0.741$ . <sup>c</sup>Imaginary frequencies obtained in the harmonic vibrational frequency analysis.

and C<sub>4</sub> is still negligible. On the other hand, a partial negative charge develops gradually on the ketene fragment, increasing from -0.23 in TS 8a to -0.44 in 9a, confirming the ionic nature of this reaction intermediate. The HOMO is seen to closely resemble that of typical enolates, and the LUMO is essentially a  $\pi$ -anti-bonding orbital located at the "iminic" fragment of the intermediate. Since the bond index between the N<sub>1</sub> and C<sub>2</sub> atoms is abnormally low and could indicate a certain biradical-like character, we have reoptimized the structure 9a at both RHF/6-31G\* and TCSCF/6-31G\* ab initio levels of theory. We like to point out that AM1 and RHF/6-31G\* optimized structures of the intermediate 9a compare at least as well as the reactants and products do. Further inspection of the RHF/6-31G\* molecular orbitals shows that the HOMO and LUMO resemble those obtained at the semiempirical level. Full reoptimization of this structure at the TCSCF/6-31G\* level of theory suggests very little biradicaloid character as revealed by the electron occupation number of the orbitals, namely  $N(\Phi) = 1.94$  and  $N(\Phi^*) = 0.06$ . The Hessian matrix has been found positive definite. Notice that the fully optimized TCSCF/6-31G\* and the RHF/6-31G\* structures are very similar (see Table I). Aoyama et al.<sup>39</sup> have also concluded that the intermediates in the SR should have mainly zwitterionic character, although their conclusion was supported with geometric arguments. The stationary point 10a, corresponding to the cisoid rotamer of 9a, was calculated to have an AM1 heat of formation 0.9 kcal/mol higher than that of 9a and was found to be a local minimum. However, the harmonic analysis of 10a computed with the MNDO method showed one imaginary frequency of 93.0i cm<sup>-1</sup> associated with the out-of-plane torsion of C<sub>3</sub> and C<sub>4</sub>. Therefore, this possible transition state should be associated with rotation about the N<sub>1</sub>-C<sub>2</sub> bond rather than with the formation of the C<sub>3</sub>-C<sub>4</sub> bond that generates the  $\beta$ -lactam ring. A related transition state has been found by Bottoni et al.<sup>37c</sup> in their MCSCF study on the cycloaddition reaction between ketene and ethylene.

The transition state 11a corresponding to the  $\beta$ -lactam ring closure was found at  $d_{12} = 1.453$  Å and  $d_{34} = 2.331$  Å in the AM1/RHF potential energy surface (see Table I). Its AM1 calculated activation enthalpy with respect to the long-range interaction adduct is 17.6 kcal/mol (the MNDO value is 19.3 kcal/mol), and its imaginary frequency confirmed that it is associated with the C<sub>3</sub>-C<sub>4</sub> bond formation process. This transition state has been calculated to be nonplanar, and its overall geometric features similar to those of the transition states reported by Houk et al.<sup>40</sup> for electrocyclic conrotatory processes. However, the electronic structure of the transition state 11a differs from those responsible for classic conrotatory electrocyclic processes. Therefore, the ring closure step can be alternatively viewed as intramolecular nucleophilic addition of the enolate fragment to the N<sub>1</sub>-C<sub>4</sub> double bond, similar to an intramolecular aldol-type reaction, in which there occurs an electrostatic and orbital interaction between the enolate-like C<sub>3</sub> atom and the electrophilic C<sub>4</sub> carbon attached to the nitrogen, leading to formation of a structural  $\sigma$  bond. From a geometrical point of view, this corresponds to a structure similar to that of a conrotatory process, probably because of steric and stereoelectronic reasons rather than orbital symmetry considerations. The transition state 11a was recalculated at UHF and 3X3CI-half-electron (HE) levels of theory, and it was found to possess quite a biradicaloid character. Thus, the difference in heats of formation between the RHF and 3X3CI-HE results was found to be 24.2 kcal/mol. Results from ab initio full optimizations of 11a at the RHF/6-31G\* and TCSCF/6-31G\* levels are also shown in Table I. As can be observed by inspection of Table I, the ab initio and semiempirical

(39) Aoyama, H.; Sakamoto, M.; Kuwabara, K.; Yoshida, K.; Omote, Y. *J. Am. Chem. Soc.* **1983**, *105*, 1958.(40) (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (c) Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708. (d) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125. (e) Buda, A. B.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 2264.

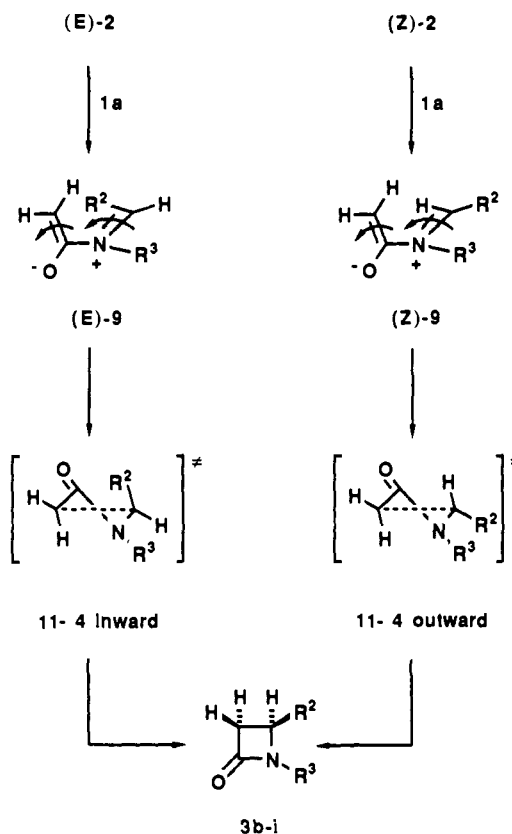


**Figure 4.** Energy profile of Staudinger reaction between ketenes and imines, and graphical definition of the main energetic and geometrical variables.

RHF optimized structures and the *ab initio* TCSCF and AM1 3×3CI-HE data compare well. Inspection of their corresponding vibrational frequencies showed only one imaginary frequency, which was confirmed to be associated with the C<sub>3</sub>-C<sub>4</sub> conrotatory bond formation process. The biradical-like character of **11a** was confirmed by the TCSCF/6-31G\* results. Thus, the electron occupation numbers of the orbitals were calculated to be  $N(\Phi) = 1.39$  and  $N(\Phi^*) = 0.61$ , and the energy was 32.6 kcal/mol lower with respect to the RHF calculation. The enthalpy of activation at the TCSCF/6-31G\* level of theory is 7.31 kcal/mol. Nevertheless, semiempirical methods are well known to give CI-HE enthalpies for pure biradicals that are systematically too negative by ca. 20 kcal/mol.<sup>41</sup> Therefore, the corresponding correction for a biradicaloid species has to be estimated. Because of the lack of experimental data, we will rely on our *ab initio* calculations. A rough estimation might be the addition to the CI-HE enthalpy of **11a** the enthalpy necessary to reproduce the enthalpy of activation obtained by the TCSCF/6-31G\* method. A simple manipulation of the data in Table I leads to an estimated value of 11.3 kcal/mol for  $T = 298$  K.

Finally, we would like to point out that recent RHF *ab initio* calculations<sup>42</sup> of **1a** + **2a**, which appeared after our work was submitted, revealed that the description of the mechanism of the SR depends strongly on the basis set used. A correct description of the reaction mechanism is provided only with the 6-31G\* or superior basis sets. Therefore, given that AM1 results compare well with *ab initio* ones, in the following sections, which deal with the effect of substituent, semiempirical AM1 will be used

**Scheme III<sup>a</sup>**



<sup>a</sup>Only one enantiomer is drawn.

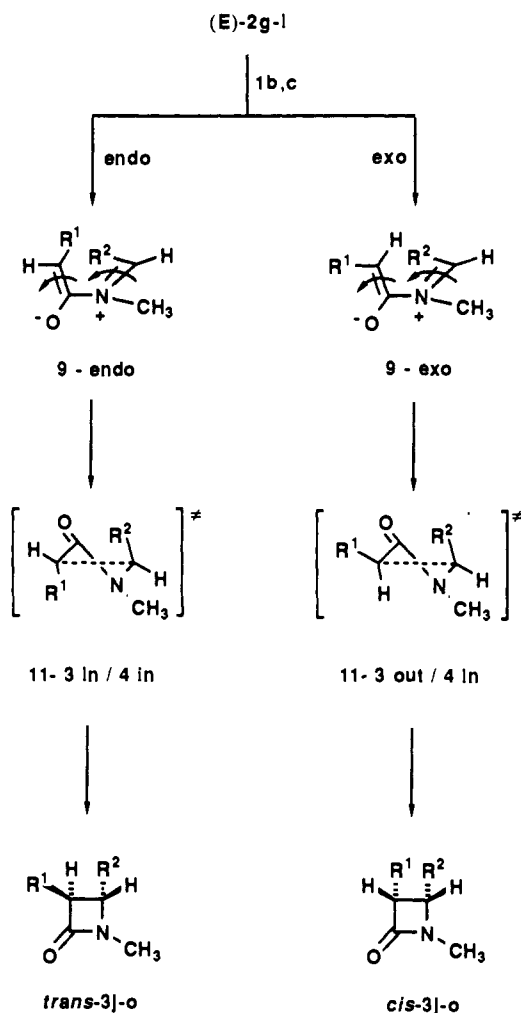
throughout instead of the otherwise computationally costly *ab initio* methods.

**Reaction between Ketene and Aldimines. The Imine Effect.** Once the principal features of the reaction between **1a** and **2a** to form the simplest  $\beta$ -lactam **3a** had been established, the next objective was to study the interaction between ketene (**1a**) and aldimines **2b-i** in order to evaluate the effect of substituents at positions 1 and 4 in the formation of  $\beta$ -lactams. Since the aldimines **2b-i** can exist (or coexist) in (*E*) and (*Z*) isomeric forms, both possibilities were considered. The selected imines **2** are indicated in Chart II. The calculations were performed with the AM1 Hamiltonian, and the main geometrical and energetic variables are outlined in Figure 4.

Inspection of the geometrical features of the transition states **8b-i** (Table V of the supplementary material) reveals that the distance between the N<sub>1</sub> and C<sub>2</sub> atoms is ca. 1.8 Å, similar to that found in **8a**. In general, these transition states are more advanced in the case of N-methylated imines **2f-i**. On the other hand, the  $d_{12}$  distances are, in general, shorter in the case of (*Z*) imines, probably because of a minor steric interaction between the positions contiguous to C<sub>3</sub> and C<sub>4</sub>. Also, it can be seen that the dihedral angle  $\omega$  formed by N<sub>1</sub>-C<sub>2</sub>-C<sub>3</sub>-C<sub>4</sub> can vary from ca. 40 to 180°. The chief geometrical characteristic of zwitterionic intermediates **9b-i** (Table VI of the supplementary material) is that the dihedral angle  $\omega$  in the case of (*Z*) imines is very close (and in some cases equal) to 180°, indicating a transoid conformation, whereas values of  $\omega$  for the adducts formed from (*E*) imines are in a wide range. However, the principal differences with respect to the case of reaction between **1a** and **2a** were found in the transition states **11b-i**, leading to formation of the C<sub>3</sub>-C<sub>4</sub> bond. Thus, the  $\Delta H_2^{\ddagger}$  values reported in Table V of the supplementary material indicate that there is no appreciable variation in the case of 4-methyl  $\beta$ -lactams **3b** and **3f** with respect to **3a**, whereas in the remaining cases the values of  $\Delta H_2^{\ddagger}$  are lower. Another interesting result is that the calculated values of  $\Delta H_2^{\ddagger}$  depend upon the configuration of the imine **2**. Thus, in the case of **3b** and **3f**, both with a methyl group at C<sub>4</sub>, the calculated values

(41) (a) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771. (b) Dannenberg, J. J.; Tanaka, K. *J. Am. Chem. Soc.* **1985**, *107*, 671. (c) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1987**, *109*, 5893.

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

Scheme IV<sup>a</sup>

<sup>a</sup> Only one enantiomer is drawn.

for  $\Delta H_2^\ddagger$  are lower for (*Z*) imines, whereas the inverse result was obtained for 3c-e, 3g, and 3i. In particular, the (*E*) imines 2e and 2i led to the lowest values of  $\Delta H_2^\ddagger$ . These results can be explained by taking into account the  $\pi$ -donor or  $\pi$ -acceptor character of the substituents and the two possible geometries of the transition states 11, drawn in Scheme III. According to the terminology established by Houk et al.,<sup>40</sup> there are two non-equivalent positions of the substituents at C<sub>4</sub>. Thus, we can consider that the R<sup>1</sup> substituent is either in an inward or an outward position with respect to the  $\beta$ -lactam ring,<sup>43</sup> depending upon the (*E*) or (*Z*) geometry of the starting imine (see Scheme IV). These geometrical dispositions at the transition states 11b-i minimize the torsion of the double bond. By analogy with the theory developed by Rondan and Houk,<sup>40b</sup> both geometries are of different energy because of the perturbation induced by the substituents at C<sub>4</sub>. As a consequence, when R<sup>2</sup> is a donating substituent, the value of  $\Delta H_2^\ddagger$  is lower for the outward mode. This is the case for the 4-methyl  $\beta$ -lactams 3b and 3f. The situation changes completely when the C<sub>4</sub> substituent has acceptor character, and therefore the calculated values of  $\Delta H_2^\ddagger$  are lower for the inward-type transition states derived from (*E*) imines having R<sup>2</sup> vinyl, phenyl, or formyl substituents. It should be noted that the 4-formyl  $\beta$ -lactams 3e and 3i derived from (*E*)-3e and (*E*)-3i, respectively, gave the lowest values of  $\Delta H_2^\ddagger$  due to the strong  $\pi$ -acceptor character of the formyl group. Moreover, these values

(43) Although the notation introduced by Houk refers to the cycloreversion of cyclobutenes to butadienes and our study involves the reverse transformation, we have kept Houk's original terminology in order not to confuse the meaning of the "inward" and "outward" terms. An unambiguous alternative could be to use the terms "inner" and "outer", respectively.

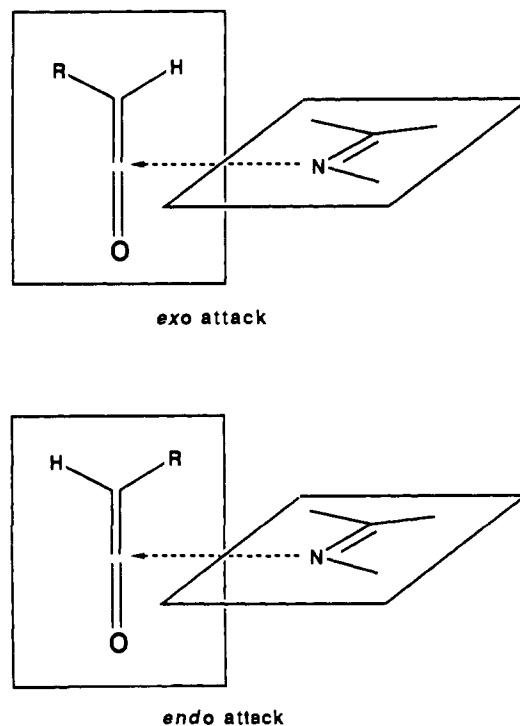


Figure 5. Schematic representation of the two possible initial approaches between an imine and a unsymmetric ketene. Only one enantiomer is drawn.

are probably even lower because of the error introduced in the RHF description, *vide infra*. This result is in agreement with the experimental evidence that imines derived from glyoxal and glyoxalates are very reactive and lead to  $\beta$ -lactams even in reaction with unactivated ketenes.<sup>44</sup>

Since significant biradical-like character was found for the TS 11a corresponding to the simplest case, we performed single-point 3 $\times$ 3CI-HE calculations for the TSs 11b-i. The difference in heat of formation between the RHF and 3 $\times$ 3CI-HE results is tabulated as the  $\delta\Delta H$  parameter in Table VII of the supplementary material and can serve as an indication<sup>41c</sup> of the biradical character of these TSs. In all cases the  $\delta\Delta H$  values were lower than in 11a and ranged from 6.3 to 11.9 kcal/mol. These values are usually considered over the limit between closed-shell and biradical species.<sup>41</sup> Moreover, our estimation of the correction term of the energy in 11a is quite similar to the  $\delta\Delta H$  values obtained. Therefore, the biradical-like character of these TSs should be lower than in 11a, and the  $\Delta H_2^\ddagger$  values can be considered as reasonably accurate, since the error involved in the RHF description is lower in more extended systems.<sup>41c</sup> The exceptions were the TSs 11e and 11i, both having formyl groups at C<sub>4</sub>. In these cases, the  $\delta\Delta H$  values were found to be in the range of 13.5-15.2 kcal/mol. This means that the biradical character of these TSs is significantly higher than in the remaining cases. This result is in agreement with chemical intuition, since a positive charge at the  $\alpha$ -position of a carbonyl group is considerably less favored than a radical species.

**Reaction between Substituted Ketenes and Imines. Ketene Effect and Stereoselectivity.** In the preceding section it was established that the formation of a  $\beta$ -lactam via the SR can take place through two different transition states leading to the ring closure, depending upon the (*E*)/(*Z*) stereochemistry of the starting imine. Therefore, it now remains to evaluate the effect of an unsymmetrically substituted ketene on the principal parameters of the SR as well as the influence of the different approaches and starting geometries

(44) For leading references, see: (a) Palomo, C.; Ontoria, J. M.; Odriozola, J. M.; Aizpurua, J. M.; Ganboa, I. *J. Chem. Soc., Chem. Commun.* **1990**, 248. (b) Palomo, C.; Cossio, F. P.; Odriozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1991**, *56*, 4418. (c) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M. *J. Org. Chem.* **1992**, *57*, 1571.



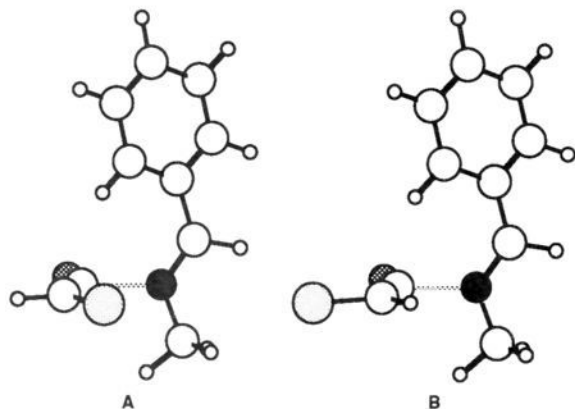


Figure 6. Computer plot (AM1/RHF results) of the calculated transition states **8** for the interaction between chloroketene (**1c**) and (*E*)-*N*-methylbenzylideneamine (*E*)-**2h**. (A) Endo attack; (B) exo attack.

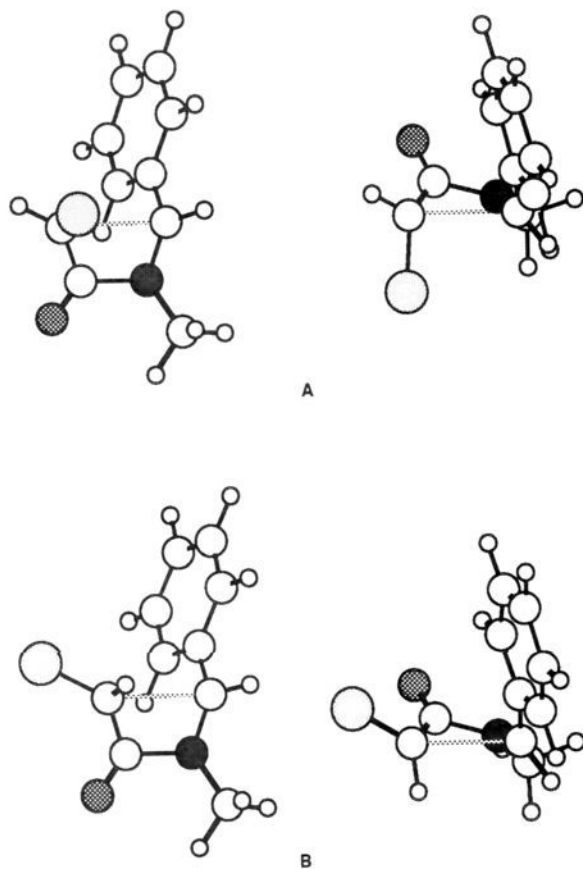


Figure 7. Computer plot (AM1/RHF results) of the calculated transition states **11** for the reaction between chloroketene (**1c**) and (*E*)-*N*-methylbenzylideneamine (*E*)-**2h**. (A) (3-in/4-in) ring closure leading to the trans  $\beta$ -lactam **3k**; (B) (3-out/4-in) ring closure leading to *cis*-**3k**.

on the stereochemistry of the resulting  $\beta$ -lactams.

The interaction between an unsymmetrically substituted ketene and an imine leading to the formation of the corresponding zwitterionic intermediate **9** via N–C bond formation can conceivably take place in two different ways, as depicted in Figure 5. In one of them, denoted "exo", the imine molecule approaches the ketene from the direction opposite the ketene substituent. In the alternative interaction mode, denoted "endo", the imine approach takes place through the region occupied by the ketene substituent. In principle, as has been pointed out by Hegedus,<sup>13</sup> it is expected that exo approach will be favored over the endo mode due to steric factors. This hypothesis was confirmed when the interactions between methylketene (**1b**) and imines **2g–i** in both

(*Z*) and (*E*) configurations were studied. Thus, the corresponding transition states **8** showed a higher activation barrier for endo approach. As can be seen by inspection of Table XII of the supplementary material, the  $\Delta\Delta H_1^\ddagger = \Delta H_1^\ddagger(\text{exo}) - \Delta H_1^\ddagger(\text{endo})$  values are less than  $-1.4$  kcal/mol. However, the result was the opposite when the interaction between chloroketene (**1c**) and (*E*)/(*Z*)-*N*-methylaldimines **2g–i** was studied. In this case, the activation barriers  $\Delta H_1^\ddagger$  were higher for exo approach. Moreover, the  $\Delta\Delta H_1^\ddagger$  values are positive, lying in the range of 0.4–2.0 kcal/mol (see Table XII of the supplementary material). This result can be explained by the assistance of the chlorine lone pairs over the partial positive charge which is being generated at the nitrogen atom. Thus, the electrostatic attractive interaction between chlorine and nitrogen atoms in the endo transition state, favored by the orthogonal approach of both partners, with a Cl–N distance of ca. 2.98 Å, results in a stabilizing effect not accessible through the exo approach. As a consequence, a lower activation barrier is obtained for the endo transition state **8**. These considerations can be easily visualized in Figure 6, in which the exo and endo transition states between chloroketene and (*E*)-*N*-methylbenzylideneamine (**2h**) are depicted. In general, as can be seen in the data listed in Table IX of the supplementary material, the exo transition states were found to be more advanced than the endo ones, resulting in smaller distances  $d_{12}$  and greater angles  $\alpha$ . This result is consistent with minor steric interactions between ketene and imine substituents in the exo approach. On the other hand, the  $\Delta H_1^\ddagger$  values obtained for the transition states **8** derived from reaction of chloroketene are lower than the  $\Delta H_1^\ddagger$  values derived from methylketene. This result is in good agreement with the fact that the SR works better when there are electronegative substituents bearing lone pairs in the starting ketene.<sup>3,12</sup> The use of alkylketenes requires more drastic reaction conditions<sup>12c</sup> or the presence of very active imines such as those derived from glyoxals and glyoxalates<sup>44</sup> (vide supra). These results can be easily explained by means of simple perturbational arguments on the effect of the substituents on the frontier orbitals of the ketene.<sup>10</sup> Thus, the presence of a chlorine atom in **1c** induces relative stabilization of ketene's (**1a**) LUMO by ca. 0.69 eV, whereas the methyl group of **1b** leads to a relative increment of ca. 0.37 eV. As a consequence, **1c** is more susceptible to nucleophilic attack by the corresponding imine.

The same trends shown in the structures and energies of the transition states **8** are observed in the corresponding zwitterionic intermediates **9** (Table X of the supplementary material). Thus, the heats of formation corresponding to the endo derivatives having a chlorine atom are lower than those of the exo adducts, whereas the reverse situation is observed in the intermediates derived from methylketene (**1b**).

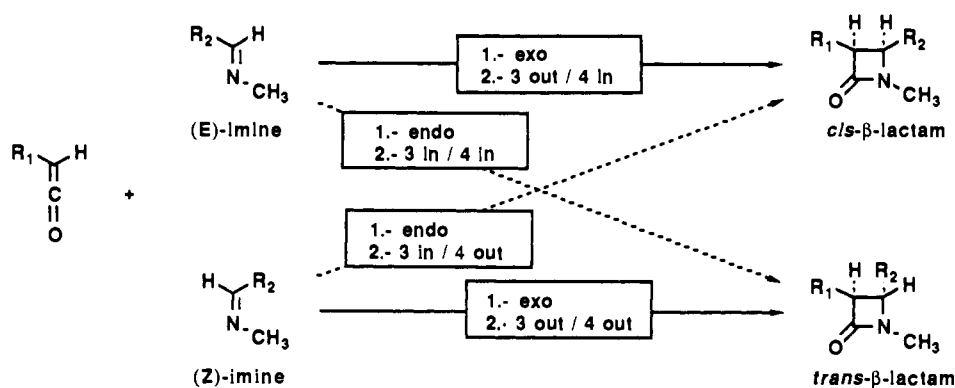
The above results introduce a considerable complication in the stereochemical course of the whole reaction, and perhaps the difficulties found in explaining the stereochemistry of the SR have their origin in this fact. However, in ketenes having bulky substituents, the steric effects could predominate over the electronic interactions, probably resulting in a general validity of the Hegedus model.

The corresponding transition states **11**, Scheme IV, leading to *cis* or *trans*  $\beta$ -lactams **3i–o**, also show marked differences depending upon both the (*E*)/(*Z*) geometry of the starting imine **2** and the endo/exo approach of the ketene partner. In the case of (*E*) imines, conrotatory ring closure leads to *trans*  $\beta$ -lactams starting from endo adducts **9**, whereas the exo zwitterionic intermediates give the corresponding *cis*  $\beta$ -lactams. Thus, the fact that the SR between chloroketene and aldimines leads to the formation of *trans*  $\beta$ -lactams<sup>45</sup> must be due to preferential endo attack in the first step of the reaction.<sup>46</sup> As can be seen, the transition state **11** leading to the *trans*  $\beta$ -lactam incorporates the substituent at position 3 in an inward disposition with respect to

(45) (a) Nelson, D. A. *J. Org. Chem.* **1972**, *37*, 1447. (b) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, 3167.

(46) Recently, Brady et al. have proposed the preferential endo approach in the reaction of (*N*-alkyl-*N*-phenylamino)ketene with imines: see Brady, W. T.; Dad, M. M. *J. Org. Chem.* **1991**, *56*, 6118.



Scheme V<sup>a</sup>

<sup>a</sup> Only one enantiomer is drawn.

the  $\beta$ -lactam ring. Analogously, this substituent is in an outward orientation in the case of transition state **11**, leading to the corresponding cis isomer. In both cases the substituent at the C<sub>4</sub> position is in an inward disposition, since both transition states have been generated from (*E*) imines (vide supra). The activation barriers  $\Delta H_2^\ddagger$  as well as the corresponding  $\Delta\Delta H_2^\ddagger = \Delta H_2^\ddagger(\text{cis}) - \Delta H_2^\ddagger(\text{trans})$  differences are given in Table XII of the supplementary material. Inspection of these data reveals that in all the cases studied the transition states **11** leading to cis  $\beta$ -lactams are always of lower energy than the corresponding ones leading to the trans isomers. Thus, the transition state **11** derived from the interaction between (*E*)-*N*-methylbenzylideneamine ((*E*)-**2h**) and ketenes **1b** and **1c** gives  $\Delta\Delta H_2^\ddagger$  values of -3.3 and -6.6 kcal/mol, respectively, both favoring the formation of *cis*-**3n** and *cis*-**3k**. The values of  $\Delta H_1^\circ$  reveal that, as expected, thermodynamic control favors formation of the trans isomers, i.e., those with the bulky substituents away from each other. Therefore, the existence of lower values for the energy barriers  $\Delta H_2^\ddagger$  corresponding to the formation of cis  $\beta$ -lactams cannot be rationalized on the basis of steric arguments. Instead, the explanation proposed by Houk et al.<sup>40</sup> for the stereochemistry of the conversion of cyclobutenes into butadienes can also be extended to the formation of the  $\beta$ -lactam ring via formation of the C<sub>3</sub>-C<sub>4</sub> bond. It is well known that both chlorine and methyl substituents have donor character, the methyl group being the weakest donor of the alkyls. Therefore, applying the perturbational arguments exposed for the substituents at C<sub>4</sub> to the present case, it can be concluded that both chlorine and methyl groups "prefer" to rotate outward. Since the C<sub>4</sub> substituents rotate inward because of the initial (*E*) configuration of the starting imine (see Scheme IV), the more favored transition state corresponds to outward rotation of the C<sub>3</sub> substituents, leading to preferential formation of the cis  $\beta$ -lactam. These arguments are consistent with the geometrical features (see Table XI of the supplementary material) of these transition states. Thus, the 3-outward are more advanced transition states, having shorter distances  $d_{34}$ . These results can be easily visualized in Figure 7, which depicts two views corresponding to the 3-out/4-in and 3-in/4-in transition states **11** associated with the interaction between (*E*)-*N*-methylbenzylideneamine (**2h**) and chloroketene (**1c**), leading to *cis*- and *trans*-**3n**, respectively. Note that the conformation of the phenyl group is such as to maximize the effect of the  $\pi$ -aryl moiety over the p interacting orbitals of the C<sub>3</sub> and C<sub>4</sub> atoms. Therefore, the reaction of (*E*) imines with unsymmetrical ketenes in general leads to the formation of cis  $\beta$ -lactams. The only complication, neglecting isomerization processes, arises from the preferential stereoselectivity derived from the formation of the C-N bond (vide supra). Moreover, these results explain the fact that bulky substituents at either N<sub>1</sub> or C<sub>4</sub> positions favor the formation of cis  $\beta$ -lactams,<sup>11j,12</sup> since this results in a predominance of the (*E*) isomer.

In the case of (*Z*) imine the reverse situation exists, since the C<sub>4</sub> substituent is in an outward disposition, imposed by the (*Z*) configuration of the starting imine, whereas the C<sub>3</sub> substituent again "prefers" to rotate outward. Therefore, the transition states

**11** (3-out/4-out), leading to the formation of trans  $\beta$ -lactams, are of lower energy than the corresponding ones **11** (3-in/4-out). This last result is again in good agreement with the experimental fact that (*Z*) imines give predominantly (or exclusively) trans isomers, as is easily achieved by blocking the (*Z*) configuration by means of a cyclic imine.<sup>17,47</sup>

As in the case of TSs **11b-i**, we have calculated the value of  $\delta\Delta H$  for the TSs **11** resulting from the interaction between ketenes **1b,c** and imines **2g-i**. The same trends as above were observed, and thus the  $\delta\Delta H$  values were in the range of 6.2-12.9 kcal/mol (see Table XI of the supplementary material). The exception was again the TSs **11** corresponding to the interaction between **1b,c** and the imine (*Z*)-**2i** ( $\delta\Delta H$  values in the range of 14.1-17.4 kcal/mol), thus confirming the higher biradical character of the TSs **11** which incorporate carbonyl groups at the C<sub>4</sub> position of the forming  $\beta$ -lactam ring.

## Conclusions

The present work has studied the different variables and approaches involved in the Staudinger reaction. The main conclusions obtained can be summarized as follows: (a) the reaction between ketenes and imines occurs in two steps; (b) the reaction takes place via the formation of a N<sub>1</sub>-C<sub>2</sub> bond, leading to a zwitterionic reaction intermediate, followed by ring closure via formation of the C<sub>3</sub>-C<sub>4</sub> bond; (c) in the second transition state the substituent at the C<sub>4</sub> position is inward with respect to the  $\beta$ -lactam ring when an (*E*) imine is used as starting material, whereas when this imine has the (*Z*) configuration, the disposition is outward; (d) the formation of cis and trans  $\beta$ -lactams depends upon the endo or exo approaches between the iminic nitrogen atom and the carbonyl group of the ketene and the relative in/out relationship between the C<sub>3</sub> and C<sub>4</sub> substituents (the possible types of interaction are depicted in Scheme V); and (e) in general, (*E*) imines lead preferentially to cis  $\beta$ -lactams and (*Z*) imines give predominantly the corresponding trans isomers.

Some further aspects of the reaction, such as a more detailed study on the effect of the substituents at the C<sub>3</sub> position as well as the interaction between asymmetric ketenes and imines, are actively underway in our laboratory, and the results will be published elsewhere.

**Acknowledgment.** The present work has been supported by Comisi3n Interministerial de Ciencia y Tecnologia (Project FAR:88-0393) and by Universidad del Pais Vasco/Euskal Herriko Unibertsitatea (Projects UPV 170.215-E185/90 and 203.215-E081/90). The authors gratefully acknowledge the EHU/UPV Computing Centre and Basque Country Supercomputer Centre (ESZ-CVS) for providing the necessary computer facilities. We thank Dr. Santiago Olivella, Universitat Central de Barcelona, for helpful discussions and encouragement.

(47) (a) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 4506. (b) Muller, M.; Bur, D.; Tschamber, T.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 767.

**Supplementary Material Available:** Additional details of the methodology used throughout this work; tables including the more relevant structural and energetic data of **1a-c**, **2a-i** (in both (*E*) and (*Z*) configurations), **3a-o**, **8b-i**, **9b-i**, and **11b-i** (from both (*E*) and (*Z*) imines) and stationary points **8**, **9**, and **11** corre-

sponding to different approaches between ketenes **1b,c** and imines **2g-i** in both (*E*) and (*Z*) configurations; complete ab initio data of the stationary points **9a** and **11a** computed at RHF/6-31G\* and TCSCF/6-31G\* levels of theory (17 pages). Ordering information is given on any current masthead page.

## Electrophilic Aromatic Cl<sup>+</sup> Addition and CO<sup>+</sup> Substitution in the Gas Phase

Tapio Kotiaho,<sup>†,‡</sup> Brian J. Shay,<sup>‡</sup> R. Graham Cooks,<sup>\*,‡</sup> and Marcos N. Eberlin<sup>§</sup>

Contribution from the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, and Universidade Estadual de Campinas, C.P. 6154, Campinas, SP, Brazil. Received April 20, 1992

**Abstract:** Chlorine cation addition to benzene, aniline, anisole, styrene, chlorobenzene, and nitrobenzene was studied using NH<sub>3</sub>Cl<sup>+</sup>, ClC≡O<sup>+</sup>, protonated CH<sub>3</sub>Cl, and Cl<sup>+</sup> as reagent ions. The reactions of protonated monochloramine were followed using a direct insertion membrane probe for sample introduction and a pentaquadrupole mass spectrometer for product characterization. The other reagent ions ClC≡O<sup>+</sup>, Cl<sup>+</sup>, and protonated CH<sub>3</sub>Cl were generated by electron ionization of acetyl chloride and carbon tetrachloride and by methane chemical ionization of CH<sub>3</sub>Cl, respectively. The main reactions of NH<sub>3</sub>Cl<sup>+</sup> with aromatic compounds are electrophilic Cl<sup>+</sup> and H<sup>+</sup> addition and charge exchange to form the aromatic radical cation. Reactions of ClC≡O<sup>+</sup> with aromatic compounds include (i) Cl<sup>+</sup> addition, (ii) CO<sup>+</sup> substitution for a hydrogen atom, and (iii) formation of the molecular radical cation of the substrate. The naked Cl<sup>+</sup> ion does not chlorinate aromatic compounds but does undergo charge exchange. Protonated CH<sub>3</sub>Cl also fails to add Cl<sup>+</sup> to the aromatic compounds, proton transfer being the main reaction observed. Ion/molecule reaction products were characterized by comparing sequential product ion mass spectra (MS/MS/MS) to the MS/MS product ion mass spectra of reference ions, generated by chemical ionization of appropriate chlorine-substituted compounds. The sequential product spectra collected with the pentaquadrupole instrument show that both the Cl<sup>+</sup> addition products and the CO<sup>+</sup> substitution products are σ-bonded to the aromatic compound. Comparisons with the MS/MS spectra of model ions suggest that both Cl<sup>+</sup> and CO<sup>+</sup> add principally to the para position in aniline. Reaction occurs at the same position for anisole, although contributions from reactions at other sites are not excluded. Substitution of hydrogen by CO<sup>+</sup> in aniline and anisole also proceeds principally at the para position, although it also occurs at the nitrogen of aniline. Evidence is given for Cl<sup>+</sup> binding to the β-carbon in styrene and to the ring in chlorobenzene. Nitrobenzene, the least reactive compound, gave only traces of a Cl<sup>+</sup> addition product and did not undergo substitution of CO<sup>+</sup> for hydrogen. However, it did display one unique reaction, the substitution of NO<sub>2</sub><sup>+</sup> by Cl<sup>+</sup>. The evidence provided by the MS<sup>3</sup> experiments for the site of Cl<sup>+</sup> addition was tested against—and found to be consistent with—the sites predicted to have the highest Cl<sup>+</sup> affinity by semiempirical AM1 molecular orbital calculations.

### Introduction

The importance of electrophilic aromatic substitution in solution has made it a well-studied ion/molecule reaction. Mass spectrometric methods<sup>1-6</sup> have been used in many studies of protonation<sup>1</sup> as well as alkylation<sup>1b,e,i,2</sup> and acetylation<sup>3</sup> of aromatic compounds. Higher-pressure experiments have employed radiolytic methods to study alkylation reactions of various aromatic compounds.<sup>7-12</sup>

Among the electrophilic substitution reactions, halogenation of aromatic compounds in the gas phase has received limited attention because of the lack of appropriate halogenation reagents. Chlorine cation addition to aromatic compounds in the gas phase apparently occurs in an ion trap mass spectrometer,<sup>6a</sup> but it proceeds by charge exchange with the neutral aromatic compound followed by reaction of the aromatic molecular ion with molecular chlorine. The gas-phase bromination and iodination of aromatic compounds of the type C<sub>6</sub>H<sub>5</sub>X (X = F, Cl, Br, CH<sub>3</sub>) have been investigated using Br<sup>+</sup> and I<sup>+</sup> produced by a radiolytic method.<sup>11</sup> Bromination and iodination occur but with low positional selectivity compared to the corresponding solution-phase reactions. Other authors have also reported, although incidentally, on the formation

of halogenated aromatic compounds in the gas phase.<sup>13</sup> For example, in a study on the reactions of the pyridine molecular

(1) (a) Lau, Y. K.; Kebarle, P. *J. Am. Chem. Soc.* **1976**, *98*, 7452. (b) Kruger, T. L.; Flammang, R.; Litton, J. F.; Cooks, R. G. *Tetrahedron Lett.* **1976**, *50*, 4555. (c) Pollack, S. K.; Devlin, J. L., III; Summerhays, K. D.; Taft, R. W.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 4583. (d) Maquestiau, A.; Van Haverbeke, Y.; Misproue, H.; Flammang, R.; Harris, J. A.; Howe, I.; Beynon, J. H. *Org. Mass Spectrom.* **1980**, *15*, 144. (e) Wood, K. V.; Burinsky, D. J.; Cameron, D.; Cooks, R. G. *J. Org. Chem.* **1983**, *48*, 5236. (f) Lau, Y. K.; Nishizawa, K.; Tse, A.; Brown, R. S.; Kebarle, P. *J. Am. Chem. Soc.* **1981**, *103*, 6291. (g) Liauw, W. G.; Harrison, A. G. *Org. Mass Spectrom.* **1981**, *16*, 388. (h) Houriet, R.; Schwartz, H.; Zummack, W.; Andrade, J. G.; Schleyer, P. v. R. *Nouv. J. Chim.* **1981**, *5*, 505. (i) Pachuta, S. J.; Isern-Flecha, I.; Cooks, R. G. *Org. Mass Spectrom.* **1986**, *21*, 1. (j) Mason, R.; Milton, D.; Harris, F. *J. Chem. Soc., Chem. Commun.* **1987**, 1453. (k) Fernandez, M. T.; Jennings, K. R.; Mason, R. S. *J. Chem. Soc., Faraday Trans. II* **1987**, *83*, 159. (l) McMahon, A. W.; Chadikun, F.; Harrison, A. G.; March, R. E. *Int. J. Mass Spectrom. Ion Proc.* **1989**, *87*, 275.

(2) (a) Sen Sharma, D. K.; Kebarle, P. *J. Am. Chem. Soc.* **1982**, *104*, 19. (b) Isern-Flecha, I.; Cooks, R. G.; Wood, K. V. *Int. J. Mass Spectrom. Ion Proc.* **1984**, *62*, 73. (c) Harrison, A. G. *Can. J. Chem.* **1986**, *64*, 1051. (d) Burinsky, D. J.; Campana, J. E. *Org. Mass Spectrom.* **1988**, *23*, 613. (e) Holman, R. W.; Gross, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 3560. (f) Nourse, B. D.; Brodbelt, J. S.; Cooks, R. G. *Org. Mass Spectrom.* **1991**, *26*, 575.

(3) (a) Dunbar, R. C.; Shen, J.; Olah, G. A. *J. Am. Chem. Soc.* **1972**, *94*, 6862. (b) Chatfield, D. A.; Bursey, M. M. *J. Am. Chem. Soc.* **1976**, *98*, 6492.

(4) Ausloos, P. *Kinetics of Ion-Molecule Reactions*; Plenum Press: New York, 1979.

(5) (a) Benzera, S. A.; Hoffman, M. K.; Bursey, M. M. *J. Am. Chem. Soc.* **1970**, *92*, 7501. (b) Ausloos, P.; Lias, S. G. *Int. J. Chem. Kinet.* **1978**, *10*, 657.

\* Corresponding author.

<sup>†</sup> On leave from the Technical Research Center of Finland, Chemical Laboratory, Biologinkuja 7, 02150 Espoo, Finland.

<sup>‡</sup> Purdue University.

<sup>§</sup> Universidade Estadual de Campinas.