Pergamon

0040-4039(94)01643-7

Theoretical and Experimental Studies on the Periselectivity of the Cycloaddition Reaction Between Activated Ketenes and Conjugated Imines.

**Iosune Arrastia, Ana Arrieta, Jesus M. Ugalde, and Fernando P. Cossío***

Kimika Fakultatea. Euskal Herriko Unibertsitatea. P.K. 1072, 20080 San Sebastián-Donostia. Spain.

Begoña Lecea

Farmazi Fakultatea. Euskal Herriko Unibertsitatea. Lasarteko ataria z/g. 01007 Vitoria-Gasteiz. Spain.

Abstract. Theoretical and experimental studies on the cycloaddition between methoxyketene and a model conjugated imine predict the preferential formation of the [2+2] cycloadduct. A configuration interaction level of theory is required to reproduce correctly the observed periselectivity.

It is well known that ketenes react with dienes to give exclusively vinyl cyclobutanones instead of the corresponding Diels-Alder cycloadducts[1]. However, it has been reported[2] that in certain cases the Staudinger reaction (SR) between ketenes **1** and conjugated imines (1-azadienes) **2** leads to the formation of 3,4-dihydro-2-pyridones **6** instead of the corresponding β-lactams **5** (Scheme 1). Since 2-azetidinones of type **5** are valuable intermediates in the chemical synthesis of β–lactam antibiotics[3] (mainly carbapenem compounds), it is impor-
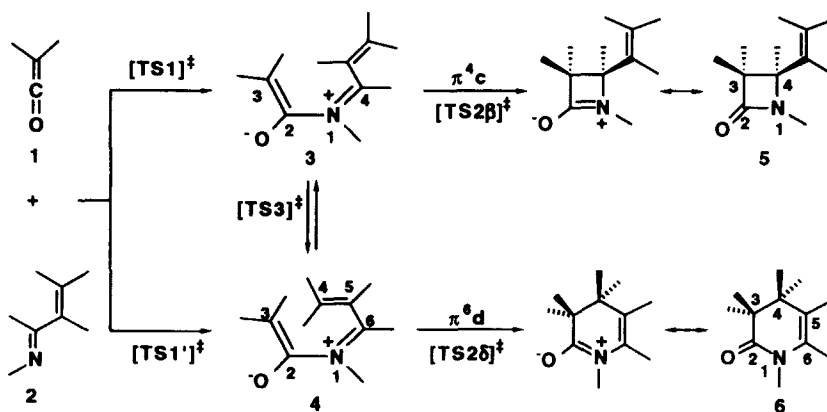
Scheme 1. The possible substituents at the different positions are not specified.

tant to understand the reasons underlying the formation of the desired [2+2] cycloadducts. Previous studies performed in our laboratory[4] have shown that the SR between ketenes and imines takes place *via* zwitterionic intermediates generated from the nucleophilic attack of the nitrogen lone pair of the imine on the carbonyl group of the ketene. According to this mechanism two different (*s-E*) and (*s-Z*) zwitterions **3** and **4** respectively can be formed (see Scheme 1). In principle, the conrotatory electrocyclization of **3** should yield the 4-vinyl-β-lactam **5**, whereas the disrotatory thermal ring closure of the intermediate **4** should lead to the corresponding δ-lactam **6**.

In previous studies[4] we have found that the AM1 semi-empirical Hamiltonian[5] gives a satisfactory description of the SR between ketenes and imines. Therefore, we decided to extend our study to the interaction between monosubstituted ketenes and 1-azadienes of type 2. In order to verify experimentally the predictions made by the calculations, we chose substrates possessing a reasonable size in order to facilitate the computation, as well as enough stability to permit the characterization of the cycloadducts eventually formed. We started our study[6] calculating the different reaction modes between (E)-N-(α-methylcinnamylidene)-methylamine[7] 2a and methoxyketene 1a, the latter being readily generated *in situ* from the dehydrohalogenation of methoxyacetyl chloride in the presence of triethylamine (Scheme 2). Figure 1 shows the energies and the main geometrical
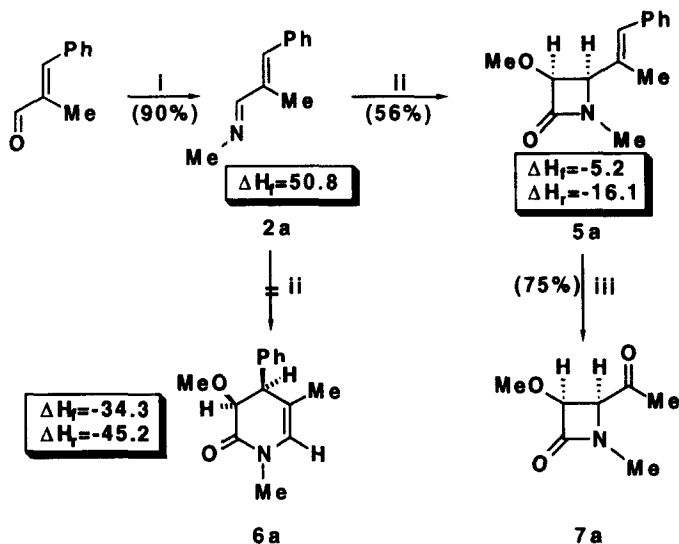
Scheme 2. Reagents and conditions: (i) MeNH$_3$$^+Cl^-$, NEt$_3$, CH$_2Cl_2$, MgSO$_4$, r.t., 12h. (ii) MeOCH$_2$COCl, NEt$_3$, CH$_2Cl_2$, -78°C→r.t., 14h. (iii) KMnO$_4$, Me$_2$CO, H$_2$O, reflux, 0.5h. Heats of formation and enthalpies of reaction have been computed using the RHF/AM1 procedure and are given in kcal/mol.

features of the transition structures TS1 and TS1', corresponding to the *exo* attack of the (s-*E*) and (s-*Z*) conformations of 2a, respectively. As expected, the formation of the N(1)-C(2) bond takes place in a non-coplanar manner[8]. The TS1' which has a cisoid conformation at the azadiene subunit, was found to be 0.9 kcal/mol more stable than its transoid analog. The enthalpy of activation for the first step of the reaction was found to be of 17.6 kcal/mol. The same energetic relationship was found for the corresponding intermediates 3a and 4a (see Figure 1). The reason for the stabilization of the cisoid conformer is the electrostatic attractive interaction between the ketene and azadiene subunits in the zwitterion 4a. The heat of formation and the main geometric features of TS3, which connect both intermediates, are depicted in Figure 1. The rotation barrier around the C(5)-C(6) bond was found to be low (3.1 and 1.4 kcal/mol from 3a and 4a respectively). Therefore, the first step of the SR between ketenes and conjugated imines does not appear to determine the distribution of the [2+2] and [4+2] cycloadducts.

The second step of the reaction consists of either the conrotatory or disrotatory electrocyclizations of 3a and 4a to give the cycloadducts 5a or 6a, respectively. Using the RHF/AM1 level of theory, the saddle points TS2β and TS2'β were readily located and characterized. As expected, TS2β, which has the substituent at
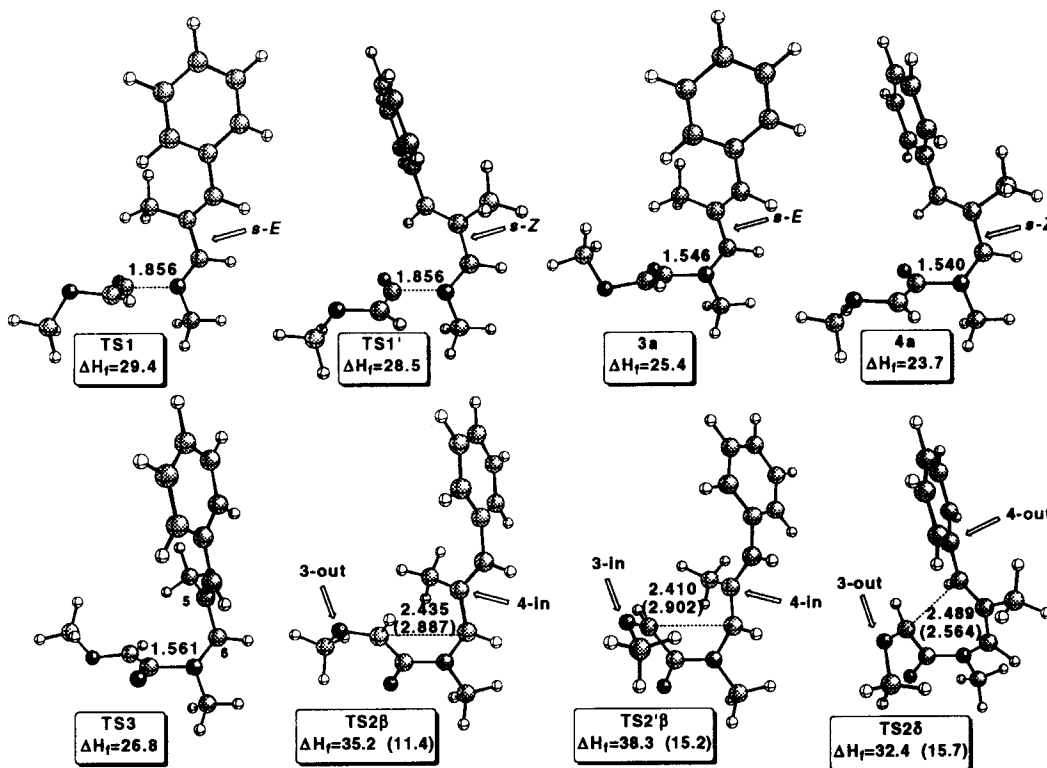
Figure 1. RHF/AM1 intermediates and transition structures for the different reaction paths of the interaction between ketene **1a** and imine **2a**. Distances and heats of formation are in Å and kcal/mol, respectively. Numbers in parentheses correspond to 3x3CI-HE/AM1 results.

C(3) in an outward disposition and hence leads to the cis-β-lactam **5a**, was found to be of lower energy than **TS2'β**. This latter TS has the C(3) and C(4) substituents inward, and as a consequence the torquoelectronic effects operating in conrotatory electrocyclizations[9] determine its higher energy (see Figure 1). However, the saddle point **TS2δ**, corresponding to the disrotatory thermal ring closure of **4a**, was also located and conveniently characterized (Figure 1). This TS has both substituents at C(3) and C(4) in an outward disposition, imposed by the exo attack in the first step of the reaction and by the (E) configuration of the olefinic double bond of **2a**, respectively. The energy of **TS2δ** was found to be 2.8 kcal/mol lower than that of **TS2β** at RHF/AM1 level of theory. In addition, the calculated heat of formation of **6a** was lower than that of **5a** and hence the enthalpy of reaction of the **1a+2a→6a** process is predicted to be 29.1 kcal/mol more exothermic than that corresponding to the formation of the [2+2] cycloadduct **5a** (see Scheme 2). Therefore, preferential formation of the δ-lactam **6a** is predicted at the RHF/AM1 level under both kinetic and thermodynamic control. However, when the saddle points **TS2β**, **TS2'β** and **TS2δ** were reoptimized at the 3x3CI-HE/AM1 level of theory, **TS2β** was found to be the lowest energy TS. All these saddle points exhibit high biradical character and the C(3)-C(4) distances are significantly higher for **TS2β** and **TS2'β** than those found at the RHF/AM1 level (see Figure 1). Since it is well known that semi-empirical methods such as AM1 give 3x3CI-HE energies for

biradicaloids that are systematically too negative[10], the enthalpies of activation at this level of theory are not accurate. However, assuming that the reaction proceeds under kinetic control[4b] and that the zwitterionic intermediates **3a** and **4a** are readily interconvertible, according to the Curtin-Hammett principle the products distribution is determined by the relative energies of the saddle points corresponding to the formation of the C(3)-C(4) bond. As a consequence, virtually exclusive formation of the *cis*-β-lactam **5a** *via* **TS2β** is predicted at 3x3CI-HE level of theory.

We have found experimentally that the SR between methoxyketene **1a** and the imine **2a** leads exclusively to the formation of the [2+2] *cis*-cycloadduct **5a**. This compound was unequivocally characterized by its spectroscopic properties[11] and by its conversion into **7a** (Scheme 2), which bears an additional non-strained carbonyl group[12]. Therefore, the 3x3CI-HE/AM1 methodology provides a correct description of the step which determines the stereoselectivity and the periselectivity of the reaction. It is interesting to note that **TS2'β**, which has the C(3) methoxy group in an inward disposition and hence should lead to the formation of *trans*-**5a**, has a heat of formation comparable to that found for **TS2δ**. According to this result, since a disubstituted ketene should bear necessarily a 3-in substituent in the TS associated with the formation of the C(3)-C(4) bond, the energy gap between the corresponding **TS2β** and **TS2δ** saddle points should diminish and eventually the trend found for a monosubstituted ketene could be inverted. This result could account for the preferred [4+2] periselectivity observed[13] in the SR between electrophilic disubstituted ketenes and conjugated imines.

References and Notes
1. (a) Brady, W.T. *Synthesis* **1971**, 415. (b) Wu, H.Y.; Walker, K.A.M.; Nelson, J.T. *J.Org.Chem.* **1994**, *59*, 1389.
2. Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Synthesis*. Trost, B., Fleming, I., Eds. Pergamon: Oxford, 1991; Vol. 5, pp 85-121.
3. Kant, J.; Walker, D.G. In "*The Organic Chemistry of β-Lactams*"; Georg, G. I., Ed.; Verlag Chemie: New York, 1993; pp 121-196.
4. (a) Cossío, F.P.; Ugalde, J.M.; López, X.; Lecea, B.; Palomo, C. *J.Am.Chem.Soc.* **1993**, *115*, 995. (b) Cossío, F.P., Arrieta, A.; Lecea, B.; Ugalde, J.M. *J.Am.Chem.Soc.* **1994**, *116*, 2085. (c) Arrieta, A.; Ugalde, J.M.; Cossío, F.P.; Lecea, B. *Tetrahedron Lett.* **1994**, *35*, 4465.
5. Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J.Am.Chem.Soc.* **1985**, *107*, 3902.
6. The calculations included in this work have been performed using the MOPAC 6.0 package: Stewart, J.J.P. *QCPE Bull.* **1983**, *3*, 101.QCPE #455. Indiana University, Bloomington, Indiana, USA. All the reactants, intermediates and products discussed in this work have positive defined Hessian matrices. The TS's which connect them have only one negative eigenvalue in their diagonalized force matrices, associated with motion along the reaction coordinate.
7. The more simple (*E*)-*N*-(cinnamylidene)-methylamine polymerizes under the reaction conditions and no cycloadducts could be obtained.
8. Cooper, R.D.G.; Daugherty, B.W.; Boyd, D.B. *Pure Appl.Chem.* **1987**, *59*, 485.
9. Houk, K.N.; Li, Y.; Evanseck, J.D. *Angew Chem.Int.Ed.Engl.* **1992**, *32*, 682.
10. (a) Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P. *J.Am.Chem.Soc.* **1986**, *108*, 5771. (b) Dewar, M.J.S.; Jie, C. *J.Am.Chem.Soc.* **1987**, *109*, 5893.
11. Selected data of **5a**: oil. IR(film, υ cm^{-1}): 1754(C=O). ^{1}H-NMR(CDCl$_3$, δppm): 7.37-7.25(m, 5H, arom.); 6.53(s$_b$, 1H, =CH); 4.65(d, 1H, J=4.6 Hz, CH *cis*); 4.23(d, 1H, J=4.6 Hz, CH *cis*); 3.47(s, 3H, OCH$_3$); 2.84(s, 3H, NCH$_3$); 1.93(d, 3H, J=1.4 Hz, CH$_3$). ^{13}C-NMR(CDCl$_3$, δppm): 167.3, 136.6, 132.6, 130.0, 128.8, 128.0, 126.7, 85.9, 66.5, 58.6, 26.7, 14.8.
12. Selected data of **7a**: oil. IR(film, υ cm^{-1}): 1750(C=O, β-lactam), 1718(C=O, ketone). ^{1}H-NMR(CDCl$_3$, δppm): 4.64(d, 1H, J=5.2 Hz, CH *cis*); 4.19(d, 1H, J=5.2 Hz, CH *cis*); 3.10(s, 3H, CH$_3$O); 2.80(s, 3H, CH$_3$N); 1.52(s, 3H, CH$_3$). ^{13}C-NMR(CDCl$_3$, δppm): 204.1 166.3, 84.9, 65.5, 58.9, 27.6, 27.5.
13. (a) Brady, W.T.; Shieh, C.H. *J.Org.Chem.* **1983**, *48*, 2499. (b) Duran, F.; Ghosez, L. *Tetrahedron Lett.* **1970**, 245. (c) Palomo, C.; Cossío, F.P.; Odriozola, J.M.; Oiarbide, M.; Ontoria, J.M. *J.Org.Chem.* **1991**, *56*, 4418.