An *Ab Initio* Study on the Mechanism of the Alkene–Isocyanate Cycloaddition Reaction to Form β-Lactams

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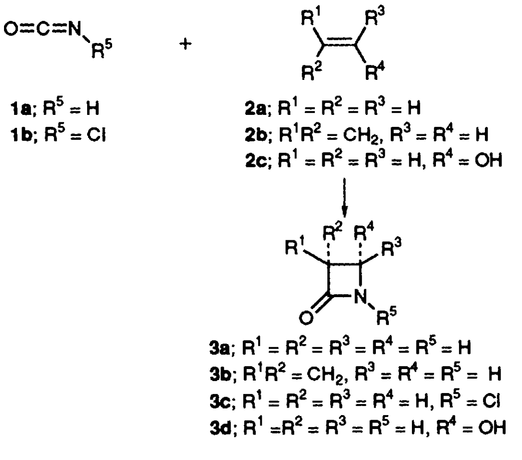
Ab initio calculations predict that the [2 + 2] reaction between isocyanates and alkenes to form β-lactams is a cycloaddition which takes place through a concerted suprafacial mechanism.

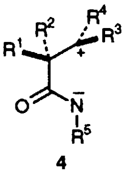
The cycloaddition reaction between isocyanates and olefins[1] or allenes[2] to form azetidin-2-ones (β-lactams) constitutes one of the most useful methods for the construction of β-lactam rings[3] (Scheme 1). Consequently, this reaction is crucial for the chemical synthesis of β-lactam antibiotics.[4] The isocyanate–alkene approach has been widely used in the synthesis of carbapenem antibiotics,[5] namely PS-5,[6] PS-6[7] and thienamycin.[8] Also, the reaction of isocyanates and allenes has been found to be useful in the synthesis of asparenomycins[9] and carpetimycins.[10]



As part of a research programme devoted to the study of the formation of β-lactams *via* cycloaddition processes by theoretical procedures,[11] we examined the reaction between isocyanate derivatives **1a, b** and alkenes **2a–c** to give the β-lactams **3a–d** (Scheme 1). These reactions could serve as simple models for the general process of formation of saturated azetidin-2-one rings and asparenomycin nuclei, respectively.

In spite of the synthetic importance of this reaction, little has been reported on its mechanism, and the literature contains a number of qualitative and contradictory considerations. Thus, in the reaction between alkenes and isocyanates the intermediates **4**[1a] and the transition structures (TSs) **5**[1c] and **6**[12] have been proposed, the latter corresponding to a classical Woodward–Hoffmann *supra–antara* mechanism.[13] Also, Moriconi[14] and then Chmielewski[15] proposed the pseudoconcerted mechanism involving the TS **7**. However, the reasons why this mechanism could take place remain unclear.

All results presented in this paper have been obtained with the GAUSSIAN90 series of programs,[16] with the 6-31G* basis



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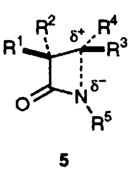

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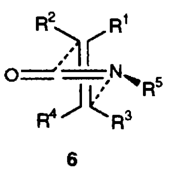

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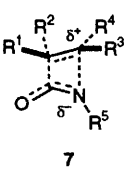

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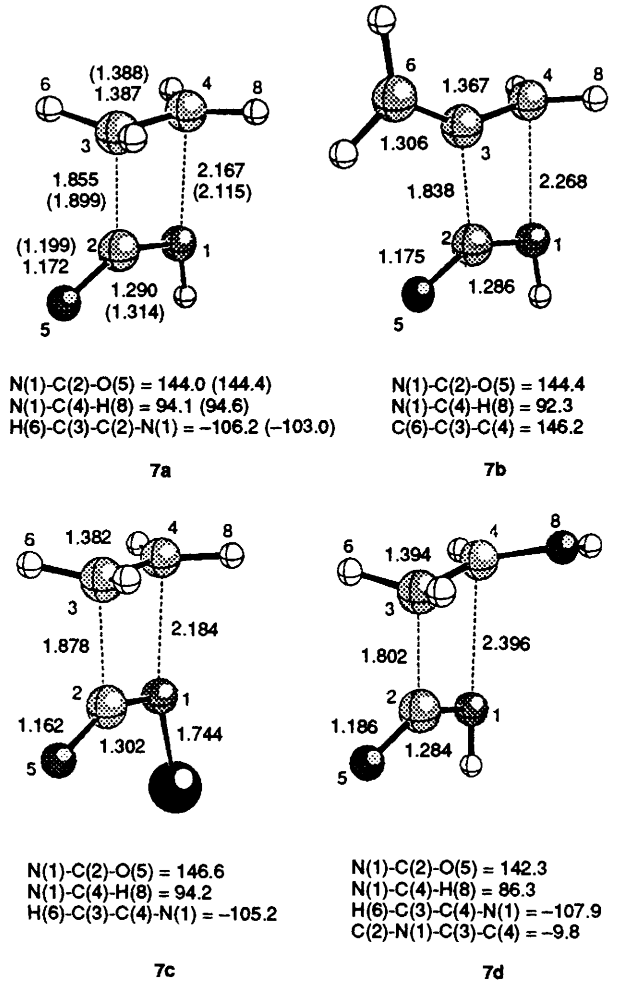
set.[17] Bond critical points and their charge densities have been calculated with the PROAIM program package.[18] Table 1 collects the calculated activation energies and reaction energies and Fig. 1 shows some selected geometric parameters of the relevant transition state structures.

Search of the singlet potential energy hypersurface to locate intermediates or TSs of type **4**–**6** was unfruitful throughout. Instead, the TSs **7a**–**d**, all of which correspond to a concerted, although asynchronous, mechanism were found.† In the case of the TS **7a** the linear arrangement in the isocyanate moiety is predicted to be substantially distorted, the N(1)–C(2)–O(5) angle being 144.0°. Also, the C(2)–C(3) and N(1)–C(4) bond distances are 1.855 and 2.167 Å, respectively (see Fig. 1). This suggests that in this TS the two σ bonds are developed to a different extent. The calculated bond orders corresponding to the C(2)–C(3) and N(1)–C(4) bonds are 0.6 and 0.3 respectively.‡ The TSs were found to be zwitterionic in character. Indeed, the isocyanate moiety of **7a** bears a net excess of 0.30 electrons, while the ethylene unit was deficient by an equal amount. This zwitterionic character was further confirmed by a single-point CASSCF(6,6)/6-31G*//RHF/6-31G* calculation on **7a**, including in the active space the six orbitals depicted in Fig. 2. The occupation numbers corresponding to the natural

Table 1 Activation energies (ΔE_a) and reaction energies (ΔE_r) obtained in the reaction between **1a**, **b** and **2a**–**c**[a]

Reaction	Level of theory	ΔE_a	ΔE_r
1a + **2a** → **3a**	RHF/6-31G*	57.1	−10.9
	RMP2/6-31G*	43.6	−15.0
	RMP4SDTQ/6-31G*	40.7	−14.1
1a + **2b** → **3b**	RHF/6-31G*	60.0	−18.5
	RMP2/6-31G*	44.9	−22.4
1b + **2a** → **3c**	RHF/6-31G*	39.5	−22.3
	RMP2/6-31G*	22.1	−29.7
1a + **2c** → **3d**	RHF/6-31G*	40.6	−13.1
	RMP2/6-31G*	30.2	−16.4

[a] The energy differences are given in kcal mol^{-1} (1 cal = 4.184 J). The geometries of reactants TSs and products were optimized at RHF/6-31G* level. [b] The total energies (a.u.) of the reactants, products and TSs are: **1a** −167.76138 (RHF/6-31G*), −168.21681 (RMP2/6-31G*), −168.24302 (RMP4SDTQ/6-31G*). **1b** −626.59828 (RHF/6-31G*), −627.18263 (RMP2/6-31G*). **2a** −78.03172 (RHF/6-31G*), −78.28434 (RMP2/6-31G*), −78.31806 (RMP4SDTQ/6-31G*). **2b** −115.86110 (RHF/6-31G*), −116.23307 (RMP2/6-31G*), −116.27907 (RMP4SDTQ/6-31G*). **2c** −152.88539 (RHF/6-31G*), −153.31462 (RMP2/6-31G*). **3a** −245.81043 (RHF/6-31G*), −246.52507 (RMP2/6-31G*), −246.58358 (RMP4SDTQ/6-31G*). **3b** −283.65193 (RHF/6-31G*), −284.48559 (RMP2/6-31G*). **3c** −704.66560 (RHF/6-31G*), −705.51428 (RMP2/6-31G*). **3d** −320.66761 (RHF/6-31G*), −321.55766 (RMP2/6-31G*). **7a** −245.70206 (RHF/6-31G*), 246.43167 (RMP2/6-31G*), −246.49617 (RMP4SDTQ/6-31G*). **7b** −283.52685 (RHF/6-31G*), −284.37831 (RMP2/6-31G*). **7c** −704.56699 (RHF/6-31G*), −705.43178 (RMP2/6-31G*). **7d** −320.58203 (RHF/6-31G*), −321.48321 (RMP2/6-31G*).



N(1)-C(2)-O(5) = 144.0 (144.4)
N(1)-C(4)-H(8) = 94.1 (94.6)
H(6)-C(3)-C(2)-N(1) = −106.2 (−103.0)

7a

N(1)-C(2)-O(5) = 144.4
N(1)-C(4)-H(8) = 92.3
C(6)-C(3)-C(4) = 146.2

7b

N(1)-C(2)-O(5) = 146.6
N(1)-C(4)-H(8) = 94.2
H(6)-C(3)-C(4)-N(1) = −105.2

7c

N(1)-C(2)-O(5) = 142.3
N(1)-C(4)-H(8) = 86.3
H(6)-C(3)-C(4)-N(1) = −107.9
C(2)-N(1)-C(3)-C(4) = −9.8

7d

Fig. 1 Selected geometric data of the RHF/6-31G* (RMP2/6-31G*) optimized transition structures **7a**–**d** corresponding to the interaction between **1a**, **b** and **2a**–**c**. Bond distances and angles are given in Å and (°), respectively. Atoms are represented in increasing order of shading as follows: H, C, N, O, Cl.

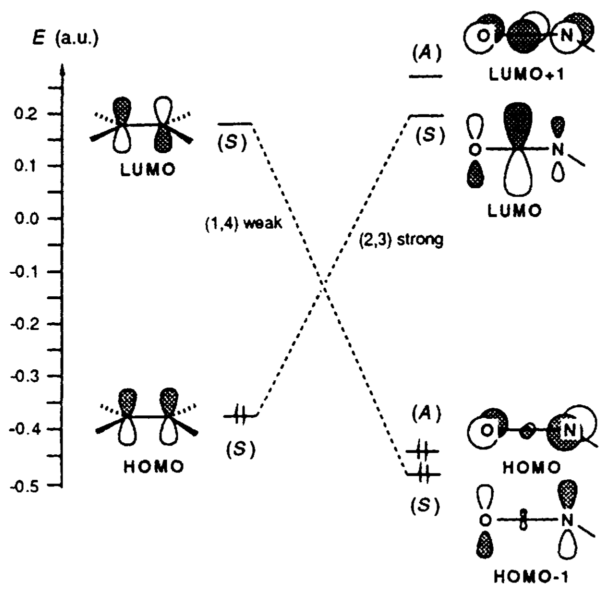


Fig. 2 Orbital interaction diagram for the reaction between an olefin and an isocyanate. (*S*) and (*A*) labels refer respectively to the symmetric or antisymmetric character of the corresponding orbitals with respect to the molecular plane of the β-lactam ring.

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† All the structures **7** showed only one negative eigenvalue in their diagonalized force matrices, and their associated eigenvectors corresponded to the reaction coordinate.

‡ These bond orders were calculated according to the following definition proposed by Bader:

$$n_{xy} = \exp\left[A_{xy}(\rho_{xy}{}^{c} - B_{xy})\right]$$

were n_{xy} is the bond order between atoms x and y, $\rho_{xy}{}^{c}$ is the critical density between them, and A_{xy} and B_{xy} are constants determined for a given basis set and a pair of atoms x and y. For a leading reference see ref. 19. The values of the constants in a.u. used in our calculations are as follows: $A_{CC} = 6.458$; $B_{CC} = 0.252$; $A_{CN} = 5.263$; $B_{CN} = 0.277$. See ref. 20.

orbitals thus obtained were found to be $N(\phi_1) = 1.971$, $N(\phi_2) = 1.960$, $N(\phi_3) = 1.910$, $N(\phi_4^*) = 0.091$, $N(\phi_5^*) = 0.040$ and $N(\phi_6^*) = 0.027$. The large charge separation found for the TSs **7** is compatible with the observed acceleration of the reaction in the presence of polar solvents.[1g] However, the most important feature of **7a** is that it has C_s symmetry. This unexpected geometry, incompatible with the classical $[_{\pi}2_s + {}_{\pi}2_a]$ approach, is again found in the TSs **7b–c**, the asynchronous character being slightly higher (Fig. 1).

The analysis of the molecular orbitals corresponding to the reactants **1** and **2**, TSs **7** and products **3** gives the clue for explaining the unusual *supra–supra* geometry of these TSs. Inspection of the interaction diagram depicted in Fig. 2 shows that the HOMO of the alkene can interact efficiently with the LUMO of the isocyanate to lead to the formation of the C(2)–C(3) bond. This interaction can be understood as a nucleophilic addition of the alkene to the carbonyl group of the isocyanate. On the other hand, the HOMO-1 of the isocyanate can interact with the LUMO of the olefin, leading to the formation of the N(1)–C(4) bond. The energy gap between these two latter orbitals is larger than in the former interaction. This accounts for the smaller development of the N(1)–C(4) bond of the TS **7**. Finally, the HOMO of the isocyanate is antisymmetric with respect to the plane of the β-lactam ring and therefore it cannot interact with the symmetric π orbitals of the alkene. Consequently, this orbital remains essentially unchanged in the TSs **7** and becomes the HOMO of the β-lactams **3**. This model predicts correctly the observed acceleration of this cycloaddition reaction,[1] when electron-withdrawing substituents and/or π-donor substituents are attached to the N(1) and C(4) sites, respectively. Thus, inspection of the data in Table 1 reveals that the activation energy of the reaction **1a** + **2a** → **3a** calculated at the RMP2/6-31G*//RHF/6-31G* level of theory is 43.6 kcal mol^{-1}. However, the corresponding values for the reactions **1b** + **2a** → **3c** [Cl at N(1)] and **1a** + **2c** → **3d** [OH group at C(4)] are 22.1 and 30.2 kcal mol^{-1}, respectively.

In summary, we have studied from a theoretical standpoint the reaction between alkenes and isocyanates to give β-lactams. The calculations predict that it is a concerted process in which both reactants interact in a suprafacial manner, and account for a number of well proved experimental facts. To the best of our knowledge, this is the first study of this kind on this important reaction.

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