THEORETICA CHIMICA ACTA

Theoret. Chim. Acta (Berl.) 54, 239–243 (1980)

Short Communications

Ab initio Study of β-Lactam Antibiotics

III. Effect of the Methoxy Substitution on the Amidic Bond Breaking of β-Lactam

Carlo Petrongolo*

Laboratorio di Chimica Quantistica ed Energetica Molecolare del C.N.R., Via Risorgimento, 35, I-56100 Pisa, Italy

Graziella Ranghino

Istituto di Ricerche "G. Donegani", Via Fauser, 4, I-28100 Novara, Italy

Ab initio SCF-MO-LCAO calculations have been performed with a *7s3p/3s* GTO basis set for the CH_3O-β-lactam + OH^- reaction which is related to the mode of action of β-lactam antibiotics. The comparison of the present results with the previous ones for β-lactam + OH^- and 3-cephem + OH^- shows that the CH_3O substitution has a negligible effect on the amidic bond breaking of β-lactam, so that this group probably influences other steps of the antibiotic reactivity of cephaloporins.

Key words: β-lactam antibiotics

1. Introduction and Procedure

In the previous papers of this series we have investigated the potential energy surfaces for the amidic bond breaking in the β-lactam + OH^- [1] and 3-cephem + OH^- [2] reactions by means of the *ab initio* Hartree–Fock method. These reactions were selected as suitable models of the similar enzymatic reaction which is the central stage of the mechanism of the antibiotic activity of cephalosporins [3]. Our results indicate that both reactions are characterized by the formation of a stable intermediate, by a barrier height equal to 15.1 and 7.0 kcal mol^{-1} for β-lactam + OH^- and 3-cephem + OH^-, respectively, and by a final product which is stabilized by an intramolecular hydrogen bond. The lower barrier height of 3-cephem + OH^- with respect to that of β-lactam + OH^- was essentially ascribed to the electron-withdrawing effect of the six-membered ring of 3-cephem, owing to the conjugation of the π orbitals of N_5 and $C_4 = C_3$ [2].

* To whom correspondence should be addressed.

0040-5744/80/0054/0239/$01.20

It is well known that several substituents of the 3-cephem core can influence the antibiotic activity of cephalosporins. We thus, in the present paper, extend our study by considering the CH_3O-β-lactam + OH^- reaction in order to investigate the effect of the CH_3O group. This substitution on C_7 (see Fig. 1) of cephalosporins yields compounds which are more resistent to the action of β-lactamase enzymes and better inhibitors of transpeptidase enzymes, although they are not necessarily more reactive towards the base hydrolysis or better antibiotics [4]. As the effect of the six-membered ring of 3-cephem is known and the essential features of the β-lactam + OH^- and 3-cephem + OH^- reactions are similar [2], we here consider the simpler CH_3O-β-lactam molecule. The calculations were performed for the most significant points of the reaction path, i.e. for the reagents, intermediate, barrier, and product, by using the optimized geometries of the points 1, 3, 6, and 15 of Ref. [1], respectively, for the β-lactam ring and a standard geometry [5] for CH_3O which was placed on the same side of the attacking OH^- ion with respect ot the β-lactam plane (see Fig. 1; this side, with $z < 0$, is called α face). The $7s3p/3s$ basis set of [2] was used in this study.

2. Results and Discussion

We report in Fig. 1 the geometries and energies of the four points of the reaction path we considered. These results clearly show that the energy changes during the β-lactam + OH^- and CH_3O-β-lactam + OH^- reactions are very similar. Indeed, CH_3O does not hinder the attack of OH^-, although these groups are on the same side, and it does not appreciably modify the barrier height for the C_8N_5 breaking and the energy of the final product. This result is strengthened by the additional information which can be obtained from the analysis of the changes of some molecular orbitals and atomic charges along the reactions. Table 1 points out that the evolution of the type and energy of the HOMO is not influenced by CH_3O and that the $2p$ orbitals of O_M contribute to the second and third HOMO of the isolated reagent, while, during the reaction, the O_M contribution is present in inner MO's (sixth and seventh HOMO's). Table 2 shows that both reactions are characterized by a similar charge transfer from O_9 and H towards N_5 and H_5, during the evolution from the intermediate to the barrier, and this charge transfer is partly reversed in the final product. Notice that the charge of CH_3O is almost constant in the intermediate-product step, so that this group has no electronic effect on the reaction.

We may thus conclude that the CH_3O substitution in β-lactam seems to have a negligible steric and electronic effect on the mechanism of the amidic bond breaking, while the six-membered ring of 3-cephem halves the barrier height. Of course, a full study of the whole reaction surfaces might lightly modify the present results by lowering, for instance, the barrier height and the product energy of the CH_3O-β-lactam + OH^- reaction for which no geometry optimization was performed. Even at this stage, however, we believe that this study yields a first theoretical approach to the understanding of the effects of some groups of cephalosporins which undergo the same base hydrolysis of the considered compounds and can react in a similar way with transpeptidase enzymes to inhibit the bacterial cell wall synthesis. Indeed our results are in accord with the experimental findings which showed that the rate

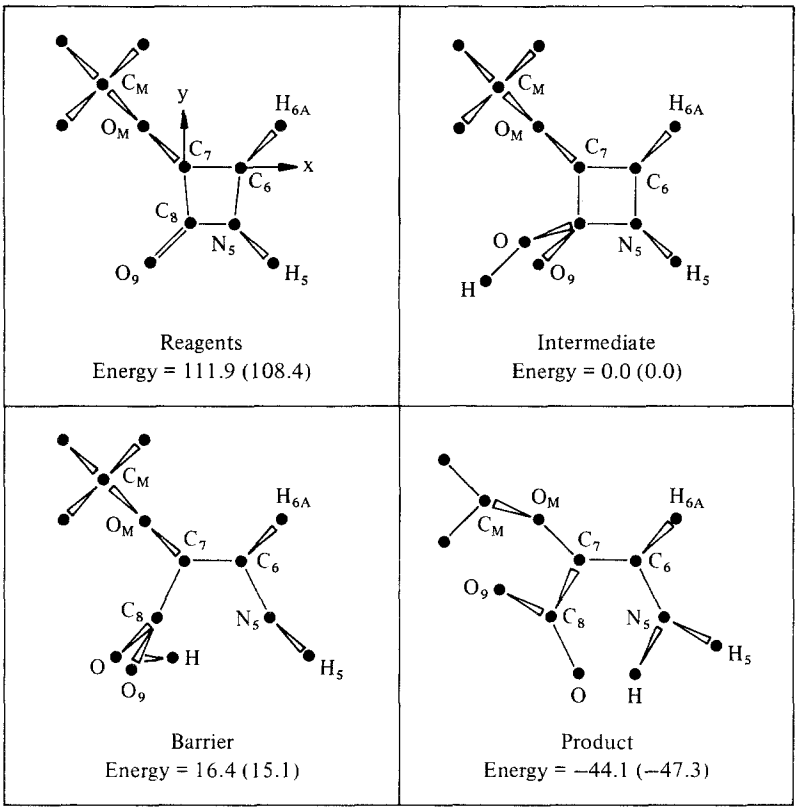

Fig. 1. CH_3O-β-lactam + OH^- reaction. *7s3p/3s* basis set. Projections on the x, y plane (defined by C_7, C_6, and N_5) of the geometries of reagents (only CH_3O-β-lactam), intermediate, barrier, and product (H_{6B} and H_7 are not shown). Energies in kcal mol^{-1} (the total energy of the intermediate is equal to −433.48032 hartree; 1 hartree = 627.506 kcal mol^{-1}). The corresponding energies of the β-lactam + OH^- reaction [2] are shown in parentheses

constants of base hydrolysis of 7-H cephalosporins are nearly equal to those of 7-CH_3O cephalosporins [4] and much greater than those of unfused β-lactams [6]. However, our study also indicates, in some contrast with the suggestion of [4], that CH_3O does not hinder the nucleophilic attack to the α face of β-lactam and that it seems unnecessary to consider the β-face attack of OH^- (on the opposite side of CH_3O, with $z > 0$) in order to explain the reactivity data. This suggestion is supported by X-ray data [7] which show that the β face of cephalosporins is severely hindered by a RCONH group which is much larger than the CH_3O one, and by our previous results [1, 2] which suggest that the barrier for the amidic bond breaking is probably lower for an intermediate obtained from an α attack than for an intermediate obtained from a β attack (experimental evidence for an α attack is reported by [8, 9]). Thus, the effect of CH_3O on the biological activity of some cephalosporins [10] might be ascribed to other steps, before or after the amidic bond breaking (noncovalent interactions or further transformations of the product).

Table 1. CH_3O-β-lactam + OH^- and β-lactam + OH^- reactions. 7*s*, 3*p*/3*s* basis set. Features of some MO's[a]

Reaction	Point	Third HOMO	Second HOMO	HOMO	ε(HOMO)[b]
CH_3O-β-lactam + OH^-	CH_3O-β-lactam	$O_9(x-y) - O_M(x)$	$O_M(x+y)$	$N_5(x-z) + O_9(z)$	−0.4462
	intermediate	$N_5(x-y)$	$O_9(y+z) + O(z)$	$N_5(x) + O_9(x)$	−0.0997
	barrier	$O_9(y+z)$	$N_5(s-y-z)$	$N_5(x-z) + O_9(x)$	−0.0714
	product	$N_5(z) + O_9(z)$	$N_5(x-z) + O_9(x) - O(x-z)$	$N_5(x) + O(x)$	−0.1612
β-lactam + OH^-	β-lactam	$C_7(x) - C_6(x) - O_9(z)$	$O_9(x-y)$	$N_5(x-z) + O_9(z)$	−0.4421
	intermediate	$N_5(x-z) + O_9(y)$	$O_9(y+z) + O(z)$	$N_5(x) + O_9(x)$	−0.0845
	barrier	$O_9(y+z)$	$N_5(s-y-z)$	$N_5(x-z) + O_9(x)$	−0.0637
	product	$N_5(z) + O(z)$	$N_5(x-z) - O(x-z)$	$N_5(x) + O(x)$	−0.1554

[a] The table reports the AO's having the expansion coefficients in the MO's ≥ 0.35 [b] Hartree

Table 2. CH_3O-β-lactam + OH^- and β-lactam + OH^- reactions. Group charges

Reaction	Point	N_5H_5	$C_6H_{6A}H_{6B}$	C_7H_7[a]	C_8O_9OH	$O_MC_MH_{MA}H_{MB}H_{MC}$
CH_3O-β-lactam + OH^-	reagents	−0.16	0.13	0.16	−0.96	−0.17
	intermediate	−0.27	−0.02	0.12	−0.56	−0.27
	barrier	−0.55	−0.08	0.11	−0.21	−0.27
	product	−0.47	−0.02	0.11	−0.36	−0.26
β-lactam + OH^-	reagents	−0.16	0.13	−0.01	−0.96	
	intermediate	−0.28	−0.03	−0.12	−0.57	
	barrier	−0.56	−0.08	−0.14	−0.22	
	product	−0.47	−0.02	−0.14	−0.37	

[a] $C_7H_{7A}H_{7B}$ for β-lactam + OH^-

In this paper the effect of the aqueous solvent was not considered. Although water should not greatly influence the C_8N_5 enzymatic breaking (as many enzymatic breakings of similar amidic bonds occur without an active role of water), it can noticeably modify the reaction path of the base hydrolysis before the formation of the intermediate [11], so that further studies on the solvent effect are now in progress.

Acknowledgements. The authors thank Prof. E. Scrocco and Dr. F. Salvetti for suggestions and discussions and Dr. R. Scordamaglia for discussions and computational advice.

References

1. Petrongolo, C., Ranghino, G., Scordamaglia, R.: Chem. Phys., in press
2. Petrongolo, C., Pescatori, E., Ranghino, G., Scordamaglia, R.: Chem. Phys., in press
3. Flynn, E. H.: Cephalosporins and penicillins, chemistry and biology. New York: Academic Press 1972
4. Indelicato, J. M., Wilham, W. L.: J. Med. Chem. **17**, 528 (1974)
5. Pople, J. A., Beveridge, D. L.: Approximate molecular orbital theory. New York: McGraw-Hill 1970
6. Washkuhn, R. J., Robinson, J. R.: J. Pharm. Sci. **60**, 1168 (1971)
7. Sweet, R. M., Dahl, L. F.: J. Am. Chem. Soc. **92**, 5489 (1970)
8. Gensmantel, N. P., Page, M. I.: J. Chem. Soc. Perkin II 137 (1979)
9. Martin, A. F., Morris, J. J., Page, M. I.: J. Chem. Soc. Chem. Commun. 298 (1979)
10. Nagarajan, R., Boeck, L. D., Gorman, M., Hamill, R. L., Higgens, C. E., Hoehn, M. M., Stark, W. M., Whitney, J. G.: J. Am. Chem. Soc. **93**, 2308 (1971)
11. Scheiner, S., Lipscomb, W. N., Kleier, D. A.: J. Am. Chem. Soc. **98**, 4770 (1976)

Received July 5, 1979