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Semiempirical Calculations of Substituent Effects on the Reactions of Cephem-Like β-Lactam Molecules

Jung Chull Lee, Hun-Yeong Koh, Moon-Ho Chang*, and Yoon Sup Lee†

Division of Applied Science, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 130-650, Korea
†Department of Chemistry and Center for Molecular Science, Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea
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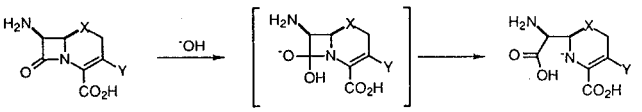
Semiempirical PM3 MO calculations are applied to estimate both 1-atom (X=S, O, C) and 3-substituent (Y=R, CH_2R, SR, CH_2SR) effects on the reactions of some 1-atom-replaced and 3-substituted cephem-like β-lactam compounds of thiacephems, oxacephems, and carbacephems. Stabilization energy (SE) of the reaction intermediate for the reaction with a hydroxyl ion can be used to evaluate the facility of a reaction and selected as a chemical reactivity index. With the 1-atom effect only , the SE values obtained imply that thiacephems are generally more reactive than the other two cephem-like molecules and the reactivity order is thiacephems>oxacephems>carbacephems. When it comes to the 3-substituent (Y=R, CH_2R, SR, CH_2SR) effect, chemical reactivity can be best realized by using a 3-substituted thiacephem molecule capable of giving a resonance-stabilized and electron-rich leaving group after the reaction with a nucleophile. SE values, however, decrease in most cases when an additional intervening ethylene group is present (Y=CH_2R, CH_2SR). The overall 3-substituent reactivity tendency is SR>CH_2SR>R>CH_2R.

Introduction

β-Lactam antibiotics are well known to inactivate several enzymes involved in the synthesis of bacterial cell walls by acylating a serine residue and still widely used in the treatment of bacterial diseases. Shortly after the first appearance of benzylpenicillin into the medicinal world at the end of the World War II, almost every effort in an attempt to study the detailed structure-activity relationships of β-lactam antibiotics was made. As a result, it was suggested that the activities of bicyclically fused β-lactam molecules were dominated by the inherent strain of the four-membered ring[1] or by amide resonance resulting from the delocalization of the nitrogen lone pair electrons to the participating atoms.[2] Amide resonance is believed to be responsible for the lower susceptibility of the carbonyl group to nucleophilic attack because it is assumed that the resonance stabilizes amides, and so an inhibition of the amide resonance would lead to increased reactivity. Therefore, synthetic chemists were, and to some extent still are, sure that more active antibiotics could be synthesized by making β-lactam systems more strained or the amide resonance more inhibited by modifying the planarity around the nitrogen. These two proposals, however, failed to explain the activity trends experimentally observed. Alternatives for reactivity indices that have been considered include C-N bond length, ^{13}C NMR chemical shift of the β-lactam carbonyl carbon atom,[3,4] IR stretching frequency of the β-lactam carbonyl group ($\nu_{C=O}$),[5] protonation ability of the nitrogen atom,[6,7] or rate of hydrolysis.[6,7] None of such factors, of course, could explain all the activity trends observed.

Cephalosporins are still being synthesized and widely studied in many drug companies and laboratories over the world. Enamine resonance is of special significance to cephalosporin systems. Many theoretical and experimental investigations on cephalosporin antibiotics have reported that cephalosporins having electron-attracting or good leaving groups at their 3'-positions increase the enamine resonance and lead to good antibacterial activities.[8] It is, however, difficult to quantitatively estimate such activity trends for the substituents at the 3'-position experimentally.

In this context, *ab initio* quantum chemical calculations could be a reliable measure. Unfortunately, because of the computational requirement, most of the molecules containing



β-lactam rings such as cephalosporins are still too large to be calculated by employing extensive and elaborate *ab initio* methods. Alternatives are semiempirical calculations. Only a limited number of calculations pertaining to cephalosporins are also possible even with a semiempirical method when the full optimization of geometry is necessary.

In this work, semiempirical calculations have been applied to the selected set of cephem-like model systems of thiacephems, oxacephems and carbacephems in an effort to find important screening factors to study a new series of β-lactam antibiotics. Previously, the stabilization energy (SE) of the reactive intermediate of each prospective reaction (Scheme 1) was calculated and selected as an opportune index for the chemical reactivity of β-lactam antibiotics.[9] SEs obtained that way can provide one critical clue to judge the activity of cephem-like β-lactam antibiotics. Encouraged by the previous results, we had performed a systematic study on 3-substituent (Y=R, CH_2R) for a series of thiacephems, oxacephems, and carbacephems through semiempirical molecular orbital calculations. In addition, a spacing sulfur atom was introduced into the 3-substituents (Y=SR, CH_2SR) in oder to study the influence of the S atom on the chemical reactivity.

Calculations

As in our preceding reports on fundamental β-lactam structures,[9,11] the semiempirical PM3 method available through MOPAC package[10] has been utilized to evaluate both 1-atom and 3-substituent effects on the reaction depicted in Scheme 1. Reactant electrophiles used in this work are 3-substituted thiacephems (X=S), oxacephems (X=O), and carbacephems (X=C). Provided that the nucleophilic hydroxide ion attacks at the β-lactam ring carbonyl carbon from the α-face of a β-lactam reactant, reactant molecule and its corresponding complex were calculated by using full geometry optimizations. The third structure in Scheme 1 was not considered in this work yet. Then the SE values were evaluated as the differences between energies of the reactants and intermediate complexes as before.[11]

When an atom is fixed at the 1-position, the terminal groups (represented by R) comprising the 3-substituent of a cephem-like molecule are classified as three types depending upon their electronic environment: acyclic simple (Y=R), acyclic extended (Y=SR), and cyclic (Y=R and SR) groups. Those terminal groups considered in this work are as follows: 16 for the acyclic simple, 12 for the acyclic extended, and 9 for the cyclic, respectively. An additional ethylene was intercalated to consider the reactivity change as an additional ethylene group intervenes into the 3-substituents (Y=CH_2R and CH_2SR).

Results and Discussion

All the SE values obtained are tabulated in Table 1 through Table 4. According to the concept of the stabilization energy of a reaction, the more negative the SE value, the more susceptible the β-lactam reactant to a nucleophile and thus the more reactive the β-lactam molecule. Therefore, SE values can be compared with one another to determine the relative theoretical reactivity of a cephem-like β-lactam reactant.

As can be seen from Table 1 to Table 4, SE values of the thiacephems are more negative and so more theoretically reactive than those of the other two cephem-like molecules, which implies that a sulfur atom is desirable at the 1-position to enhance the chemical reactivity of a antibacterial β-lactam antibiotic to be designed. This coincides well with our previous results.[11] On the contrary, the additional intervening ethylene increases the SE values for most compounds, probably due to the ability of the ethylene to hamper the elec-

Table 1. Stabilization energies (SE, kcal/mol) calculated for the reactions of thiacephems, oxacephems, and carbacephems having a variety of selected acyclic substituents at the 3-position (Y=R and Y=CH_2R)

R	Y=R			Y=CH_2R		
	X=S	X=O	X=C	X=S	X=O	X=C
-H	−93.9	−88.2	−75.2	−93.8	−88.1	−75.1
-CH_3	−93.8	−88.1	−75.1	−94.0	−88.6	−84.7
-CH_2CH_3	−94.0	−88.6	−84.7	−94.3	−85.6	−81.7
-NH_2	−92.4	−89.1	−73.0	−100.8	−98.9	−87.6
-OH	−95.2	−81.9	−76.6	−99.0	−95.4	−90.8
-OCH_3	−96.2	−93.0	−84.1	−94.4	−89.5	−84.3
-$OCOCH_3$	−103.8	−99.6	−92.9	−99.9	−95.4	−88.0
-$OCONH_2$	−103.6	−100.1	−87.0	−100.4	−97.5	−92.2
-$OCSCH_3$	−109.2	−106.1	−99.2	−108.0	−103.6	−97.4
-CHO	−111.2	−106.8	−99.9	−100.6	−96.3	−86.4
-CN	−114.5	−104.2	−100.4	−100.9	−98.1	−94.2
-F	−94.5	−93.4	−86.2	−101.0	−95.3	−86.6
-Cl	−94.7	−94.5	−89.7	−103.8	−98.8	−94.5
-N_3	−103.6	−99.9	−91.8	−105.4	−101.9	−95.9
-SH	−103.1	−101.5	−93.5	−99.3	−98.6	−92.4
-CH_2CONH_2	−103.1	−99.1	−91.0	−101.2	−97.8	−89.4

Table 2. Stabilization energies (SE, kcal/mol) calculated for the reactions of thiacephems, oxacephems, and carbacephems having a variety of selected acyclic substituents at the 3-position (Y=SR and Y=CH_2SR)

R	Y=R			Y=CH_2R		
	X=S	X=O	X=C	X=S	X=O	X=C
-H	−103.1	−101.5	−93.5	−99.3	−98.6	−92.4
-CH_3	−105.7	−101.5	−94.0	−97.3	−93.5	−86.1
-CH_2CH_3	−105.3	−101.5	−94.1	−98.8	−98.2	−91.2
-$COCH_3$	−108.4	−105.3	−98.1	−102.0	−99.1	−97.7
-$CONH_2$	−112.3	−107.5	−103.2	−105.7	−102.3	−95.8
-$CSCH_3$	−112.1	−113.5	−106.8	−105.3	−101.8	−99.4
-SH	−119.4	−114.8	−113.2	−106.5	−101.9	−95.5
-SCH_3	−116.3	−113.0	−110.6	−109.9	−107.4	−98.8
-$SCOCH_3$	−121.2	−119.1	−115.6	−108.7	−105.0	−104.3
-$SCONH_2$	−123.7	−121.8	−118.5	−110.2	−107.8	−103.1
-$SCSCH_3$	−123.8	−121.0	−118.8	−113.5	−108.0	−106.0
-CH_2CONH_2	−113.5	−106.1	−104.7	−101.6	−95.3	−89.4

Table 3. Stabilization energies (SE, kcal/mol) calculated for the reactions of thiacephems, oxacephems, and carbacephems having a variety of selected acyclic substituents at the 3-position (Y=R and Y=CH_2R)

R	Y=R			Y=CH_2R		
	X=S	X=O	X=C	X=S	X=O	X=C
	−102.3	−98.4	−91.9	−101.8	−96.7	−92.1
	−108.3	−106.7	−98.8	−106.5	−101.4	−93.9
	−105.5	−104.1	−99.2	−103.6	−102.0	−94.8
	−116.0	−111.1	−107.4	−109.7	−106.7	−98.7
	−102.8	−100.1	−93.3	−97.3	−93.2	−86.0
	−102.9	−100.5	−93.0	−97.3	−92.3	−84.8
	−111.4	−111.0	−108.7	−102.7	−97.7	−90.9
	−111.4	−109.3	−104.5	−105.5	−97.5	−89.8
	−98.0	−95.0	−88.9	−96.0	−91.3	−83.3

Table 4. Stabilization energies (SE, kcal/mol) calculated for the reactions of thiacephems, oxacephems, and carbacephems having a variety of selected acyclic substituents at the 3-position (Y=SR and Y=CH_2SR)

R	Y=R			Y=CH_2R		
	X=S	X=O	X=C	X=S	X=O	X=C
	−114.2	−110.3	−105.9	−106.5	−103.0	−101.4
	−115.6	−115.6	−112.5	−111.4	−102.1	−100.7
	−116.7	−113.6	−108.8	−111.8	−108.1	−97.3
	−120.9	−117.8	−113.7	−110.2	−106.0	−101.9
	−108.9	−105.4	−102.3	−102.0	−97.6	−95.4
	−107.3	−103.7	−98.1	−105.0	−102.1	−91.7
	−114.4	−110.2	−107.3	−113.9	−104.2	−98.0
	−113.1	−109.8	−105.5	−106.0	−101.6	−98.1
	−109.1	−105.9	−99.0	−103.2	−98.7	−89.7

tron density moving from an incoming nucleophile to the 3-substituent containing itself, destabilizing the leaving group to be generated. Exceptions are groups such as -NH_2, -OH, -F, -Cl, and -N_3 which can be rather stabilized by the intervening ethylene.

As for the 3-substituent effect, a cephem-like molecule becomes more reactive when it has an electron-pulling and simultaneously electron-abundant substituent at the 3-position to produce a resonance-flexible leaving group after the reaction with a nucleophile. This suggests, on the other hand, that a cephem-like molecule having an electron-donating and electron-poor 3-substituent which yields an unstable leaving group is theoretically less reactive.

These three effects are easily seen in Table 3 and Table 4 for a series of cyclic groups introduced to the 3-position: R, CH_2R, SR, and CH_2SR. The detailed investigation of the four tables shows that the theoretical reactivities of cephem-like molecules are cooperatively affected by 1-sulfur and 3-sulfur atoms.

Conclusions

With the 1-atom effect only, the theoretical reactivity of a thiacephem should be better than those of the other two cephem-like molecules and the estimated reactivity order goes as follows: thiacephems>oxacephems>carbacephems. This reactivity tendency is likely to be explained in terms of the 1-atom ability to accomodate the incoming electron density and stabilize the reaction complex as a nucleophile approaches the β-lactam carbonyl carbon. A sulfur atom has the greater capability to accept the incoming electron than an oxygen atom which has somewhat strong p-donating character. This means that the thiacephem system is most desirable in designing a chemically reactive cephem-like antibiotic.

Concerning the 3-substituent effect, a cephem-like molecule will become more reactive when it involves an electron-abundant and simultaneously electron-pulling group at the 3-position. However, the intervening ethylene makes a β-lactam molecule less reactive than its counterpart, except for the case of having one of the rather strong p-donating groups such as -NH_2, -OH, -F, -Cl, and -N_3 at the 3-position. Therefore, the overall reactivity order for the 3-substituents is ranked as follows: SR>CH_2SR>R>CH_2R.

Finally, this research implies that the chemical reactivity of the 3-substituted cephem-like antibiotic can be best improved by using a thiacephem system capable of giving a resonance-stabilized leaving group after the reaction with a nucleophile. This result could be useful to some synthetic chemists who are searching for new thiacephem β-lactam antibiotics.

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Synthesis and Nonlinear Optical Properties of Poly(4-nitrophenylallylamine) Derivatives

Young-Wun Kim, Kwang-Sup Lee†*, Jung-Il Jin, and Kil-Yeong Choi‡

Department of Chemistry, Korea University, 1-Anam Dong, Seoul 136-701, Korea
†Department of Macromolecular Science, Han Nam University, Taejon 300-791, Korea
‡Advanced Polymer Division, Korea Research Institute of Chemical Technology, Taejon 305-606, Korea
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A series of new NLO-active poly(4-nitrophenylallylamine) derivatives was synthesized by the nucleophilic substitution reaction of several substituted 4-nitrohalobenzenes and poly(allylamine hydrochloride). All polymers obtained were amorphous and their glass transition temperatures (T_g) were observed around 148-160 ℃. For each of these polymers, their specific T_g values were dependent on characteristic electronic structures. UV-visible absorption spectra showed maximum absorption intensity at 355-393 nm for π-π^* transition of alkylaminonitrophenyl groups. The $\chi^{(2)}$ value of poly(4-nitrophenylallylamine), as determined by the second harmonic generation at 1064 nm, for a thin polymer film poled at an elevated temperature, was 1.4×10^{-8} esu. The third-order NLO properties of poly(4-nitrophenylallylamine) derivatives were evaluated through measurement of degenerate four-wave mixing technique and $\chi^{(3)}$ coefficient in the range of $2.7\sim3.2\times10^{-12}$ esu at 602 nm was found with 400 fs laser pulses.

Introduction

Polymeric systems having nonlinear optical (NLO) active groups have attracted much scientific and technological interest because of their potential application in the field of optical communications, optical processing, and optical computing.[1] The NLO polymers could offer many advantages over the traditional inorganic substances and low molar mass organic compounds in chemical, optical, mechanical, environmental properties and cost effectiveness.[2~6] In the early research stage of polymeric NLO materials, guest-host system involving organic NLO chromophores, doped in a glassy polymer or in a liquid crystalline polymer matrix, was intensively studied.[7~13] Guest-host systems were found relatively simple to formulate. However, phase separation due to the limited solubility of chromophore in the host polymer matrix and gradual decay of orientation by thermal relaxation of poled sample have been the major obstacle for fabricating optic devices. During past several years, much efforts have been made to overcome the problem of seggregation and relaxation of chromophores by making various side chain, main chain or crosslinked polymeric systems in which the NLO chromophores were covalently incooperated into a polymer matrix.[1,14~16] Among them, the side chain polymeric systems have been considered best candidate for nonlinear optics applications, because of their ability to chromophore density, high poling efficiency and reducing optical losses. To date, literature mainly describes the side chain polymers obtained by the free radical polymerization reactions of vinyl monomers having NLO chromophores.[17~23] The main disadvantage of these type of polymers are their low molecular weights and low yields, due to the polymerization inhibition of chromophores. These problems can be solved by the polymer reaction of high molecular weight polymers having reactive groups with NLO chromophore.

This paper describes the synthesis and nonlinear optical properties of amorphous poly(4-nitrophenylallylamines) derivatives having substituted 4-nitroaniline as NLO-active side groups covalently attached to a polyethylene-type backbone, prepared by polymer reactions. The main reason for selecting polyallylamine as the polymer backbone was the ease of synthesis with high degree of functionalization possible, and high Tg, due to the direct attachment of chromophore, which is expected to increase the rigidity of the matrix and at the same time to prevent the randomization process of the oriented NLO chromophore dipoles. Third-order NLO effect of the polymeric system was also evaluate to gain understanding of NLO activity on the short range of the conjugated system.