# Semiempirical Molecular Orbital Calculations of the Substituent Effects on Acylations of 3-Cephem Analogues

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

*Division of Applied Science, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 130-650*
*†Department of Chemistry and Center for Molecular Science, Korea Advanced Institute of Science and Technology, Taejon 305-701*
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Semiempirical MO calculations are applied to estimate the substituent effects on acylations of the nonfused *N*-vinyl-2-amino β-lactams having frameworks analogous to 3-cephems. The stabilization energy for the reaction intermediate of the nucleophilic attack by the hydroxide ion is selected as the reactivity index and calculated by AM1 and PM3 methods for the model β-lactams with substituents at the C1 and *N*-vinyl terminal positions. The reactivities are larger for -SH connected to the C1 and strong π-acceptors at the *N*-vinyl terminal implying the large reactivity for known active cephalosporins. Quantum chemical calculation of stabilization energy could be useful in correlating antibiotic activities of many compounds obtained as derivatives of a lead compound.

## Introduction

Theoretical and experimental investigations on the cephalosporin antibiotics have demonstrated that the cephalosporins having electron-attracting or good leaving groups at their 3′-position display good antibacterial activities.[1-5] The activity trends for substituents at the 3′-position, however, are difficult to estimate quantitatively, but quantum chemical calculations could be useful in this regard. Especially, the stabilization energy(SE) of the intermediate for the acylation reaction is a reasonable indicator for the reactivity of the β-lactam and thus could become a useful index for the activity.[6-8] Reliable quantum mechanical calculations are best performed by employing *ab initio* methods for quantities such as molecular structures and energy differences. Unfortunately, molecules containing β-lactam rings are too large to perform extensive and systematic analysis based upon accurate *ab initio* calculations at present. Alternatives are semiempirical calculations. Even the semiempirical quantum calculations are too involved for many cephalosporins when full optimization of geometry is required for the whole molecule. In addition, systematic studies of model compounds offer better insights than the study of actual, very complicated systems. Semiempirical calculations are applied in this work to investigate the reactivity of the model systems in an effort to suggest some screening factors for the rational drug design of new series of β-lactam antibiotics. In this work, we calculate the stabilization energies(SE) of the nucleophilic reaction intermediate for the acylation reactions of model compounds, nonfused *N*-vinyl-2-amino β-lactams having some substituents at the *N*-vinyl terminal, using semiempirical MO methods with full optimization of geometries. Among the semiempirical methods available through the MOPAC package,[9] AM1 and PM3 methods[10,11] were selected here partially because of their reasonable compatibility with the *ab initio* HF/6-31G* method for geometries of two basic compounds (Figure 1) as is described in the next section. The effect of substituent is also investigated at the C1 position.

**Figure 1.** *N*-substituted 2-amino β-lactams.

## Results and Discussion

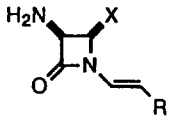
Molecular structures of two simple *N*-substituted-2-amino β-lactams, *N*-methyl-2-amino and *N*-vinyl-2-amino β-lactams in Figure 1, have been optimized by various semiempirical MO methods (MINDO/3, MNDO, AM1, and PM3) in MOPAC and by an *ab initio* method (HF/6-31G*) in Gaussian 92.[12] Selected geometrical parameters and atomic charges from the calculations are listed in Table 1 and 2. Since experimental values are not available, we will use the *ab initio* results as standards and try to find semiempirical methods that closely mimic the *ab initio* method. It is generally accepted that geometries of organic compounds are accurately computed by the HF method with 6-31G* basis sets. When structures from semiempirical calculations were superimposed with those from the *ab initio* calculations using a fitting technique in Chem-X,[13] all structures display substantial differences probably due to the deviation of torsional angles as shown in the tables. *Ab initio* structures have less pyramidal characters in the β-lactam ring than most semiempirical ones for both molecules, but MINDO/3 structure is almost as flat as the *ab initio* one. Degree of pyramidalization can be estimated from d(C5-N4-C3-C2) in the tables. Bond lengths and bond angles are in reasonable agreement among various methods. One exception may be the C-N bond length in the β-lactam ring, r(N4-C3) in Table 1 and 2, for which *ab initio* bond lengths are considerably shorter than semiempirical ones, but comparable to the value of 1.36 Å obtained for the constrained azetidin-2-one molecule by the HF/6-31G method by Sedano *et al.*[14] Most of these structural discrepan-

**Table 1.** Calculated Atomic Charges, Bond Lengths (Å), Bond and Torsion angles (°) for the *N*-methyl-2-amino β-lactam

| | MINDO/3 | MNDO | AM1 | PM3 | 6-13G* |
|---|---|---|---|---|---|
| q(C1) | 0.15 | 0.16 | −0.03 | −0.07 | −0.07 |
| q(C2) | 0.05 | 0.00 | −0.06 | −0.16 | −0.15 |
| q(C3) | 0.60 | 0.36 | 0.26 | 0.28 | 0.78 |
| q(N4) | −0.21 | −0.45 | −0.35 | −0.11 | −0.65 |
| q(C5) | 0.18 | 0.22 | −0.06 | −0.05 | −0.29 |
| q(N6) | −0.15 | −0.25 | −0.33 | −0.01 | −0.84 |
| q(O7) | −0.52 | −0.30 | −0.31 | −0.29 | −0.60 |
| r(C2-C1) | 1.53 | 1.57 | 1.58 | 1.56 | 1.55 |
| r(C3-C2) | 1.54 | 1.55 | 1.57 | 1.54 | 1.53 |
| r(N4-C3) | 1.39 | 1.42 | 1.40 | 1.47 | 1.35 |
| r(C5-N4) | 1.42 | 1.45 | 1.41 | 1.46 | 1.44 |
| r(N6-C2) | 1.42 | 1.46 | 1.42 | 1.47 | 1.44 |
| r(O7-C3) | 1.20 | 1.21 | 1.23 | 1.20 | 1.19 |
| a(C3-C2-C1) | 86.1 | 85.7 | 84.9 | 87.3 | 84.9 |
| a(N4-C3-C2) | 90.5 | 91.3 | 90.6 | 91.4 | 92.0 |
| a(C5-N4-C3) | 136.6 | 131.3 | 132.1 | 122.9 | 131.2 |
| a(N6-C2-C1) | 117.9 | 115.1 | 115.1 | 113.5 | 116.2 |
| a(O7-C3-C2) | 137.9 | 138.4 | 138.4 | 137.3 | 134.8 |
| d(N4-C3-C2-C1) | 0.3 | −4.5 | −3.5 | −6.0 | −4.3 |
| d(C5-N4-C3-C2) | −179.1 | 157.4 | 162.5 | 134.7 | 173.0 |

**Table 2.** Calculated Atomic Charges, Bond Lengths (Å), Bond and Torsion Angles (°) for the *N*-vinyl-2-amino β-lactam

| | MINDO/3 | MNDO | AM1 | PM3 | 6-13G* |
|---|---|---|---|---|---|
| q(C1) | 0.14 | 0.17 | −0.03 | −0.07 | −0.08 |
| q(C2) | 0.05 | 0.00 | −0.05 | −0.15 | −0.13 |
| q(C3) | 0.60 | 0.37 | 0.26 | 0.28 | 0.75 |
| q(N4) | −0.18 | −0.41 | −0.30 | −0.03 | −0.69 |
| q(C5) | 0.13 | 0.10 | −0.01 | −0.09 | 0.13 |
| q(C6) | −0.14 | −0.15 | −0.30 | −0.22 | −0.47 |
| q(N7) | −0.15 | −0.25 | −0.33 | −0.00 | −0.83 |
| q(O8) | −0.51 | −0.29 | −0.29 | −0.28 | −0.57 |
| r(C2-C1) | 1.53 | 1.57 | 1.58 | 1.56 | 1.55 |
| r(C3-C2) | 1.54 | 1.55 | 1.57 | 1.55 | 1.54 |
| r(N4-C3) | 1.40 | 1.42 | 1.41 | 1.46 | 1.37 |
| r(C5-N4) | 1.39 | 1.41 | 1.38 | 1.42 | 1.39 |
| r(C6-C5) | 1.33 | 1.35 | 1.34 | 1.33 | 1.32 |
| r(N7-C2) | 1.42 | 1.46 | 1.42 | 1.47 | 1.44 |
| r(O8-C3) | 1.20 | 1.21 | 1.22 | 1.20 | 1.19 |
| a(C3-C2-C1) | 86. 0 | 86.1 | 85.3 | 87.5 | 85.3 |
| a(N4-C3-C2) | 90.8 | 91.0 | 90.5 | 91.1 | 91.3 |
| a(C5-N4-C3) | 134.7 | 132.6 | 131.1 | 124.8 | 131.3 |
| aC6-C5-N4) | 130.4 | 125.0 | 125.9 | 123.4 | 125.1 |
| a(N7-C2-C1) | 118.0 | 115.2 | 117.0 | 113.5 | 117.0 |
| a(O8-C3-C2) | 137.7 | 138.7 | 136.9 | 137.6 | 136.6 |
| d(N4-C3-C2-C1) | 0.3 | −2.5 | 1.7 | −5.2 | −3.4 |
| d(C5-N4-C3-C2) | −178.8 | 172.5 | −161.6 | 141.5 | 180.1 |
| d(C6-C5-N4-C3) | 178.0 | −175.0 | 163.1 | −141.6 | −176.9 |




X = H, $CH_3$, OH, SH

R = Et, Me, $NH_2$, OH,

CHO, CN, CCH, F, SH

**Figure 2.** *N*-vinyl-2-amino β-lactams substituted at the C1 position and at the *N*-vinyl terminal for calculation of substituents effects.

cies are caused by the inability of semiempirical methods to properly describe the amide resonance of the carbonyl group with the lone pair electrons of the ring nitrogen atom. In the population analysis, nitrogen atom is more negatively charged in the HF/6-31G* calculations than in semiempirical ones.

Considering all these factors about geometry and atomic charges, it is difficult to judge which of the semiempirical methods is most close to the HF/6-31G* method. Among semiempirical methods, PM3 differs considerably from others for the values shown in the tables. Previous works imply that PM3 and AM1 are superior to other methods in reproducing experimental geometries and heats of formations.[10] Therefore, we decided to employ AM1 and PM3 methods for the present study of substituent effects on the acylation reaction for 3-cephem analogues of *N*-vinyl-2-amino β-lactams in Figure 2.

The stabilization energy is defined as the energy difference between reactants and the reaction intermediate complex for the nucleophilic attack of an hydroxide ion on the ring carbonyl carbon atom. Substituent effects at the C1 (*X* in Figure 2) as well as those at the *N*-vinyl terminal (*R* in Figure 2) are studied. Four different groups are used for *X* (=H, $CH_3$, OH, SH) in order to consider the influence of C, O, and S atoms in 3-cephems. Nine groups used for *R* may be classified according to their functional characteristics as

1) weak σ-donor : -Me, -Et
2) weak σ-acceptors and weak π-donors : -$NH_2$, -OH
3) strong π-acceptors with low-lying vacant π*-orbital : -CHO, -CN, -CCH
4) strong σ-acceptor : -F
5) weak σ-acceptor : -SH

Geometries of all reactants and intermediate complexes are fully optimized separately using both AM1 and PM3 methods. Calculated SEs for the acylations are collected in Table 3 and all are negative. In the present definition of SE where the negative SE represents stable intermediate complex, the more negative the SE value, the more reactive the β-lactam. Although AM1 and PM3 values differ substantially when substituent *R* is -CHO or -CN, the trends are in good agreement.

For a given group at the C1 position (*X* in Figure 2), β-lactams become more reactive for π-acceptors -CHO and -CN. The reactivity is not so pronounced for -CCH which can be also classified as a strong π-acceptor. The σ-acceptors also show more reactivity than σ- or π-donor implying that the acceptor property at the *N*-vinyl terminal increases the reactivity for this acylation. Rather strong reactivity of -SH is probably due to the large size of *p*-orbitals of the *S* atom in the present calculations since no *d*-orbitals are included in AM1 or PM3. The SEs for -$NH_2$ and -OH groups are

**Table 3.** Stabilization Energies (kcal/mol) for the Acylations of the *N*-vinyl-2-amino β-lactams with Substituents at the C1 and Vinyl Terminal Positions

| | $X$=H | | $X$=$CH_3$ | | $X$=OH | | $X$=SH | |
|---|---|---|---|---|---|---|---|---|
| | AM1 | PM3 | AM1 | PM3 | AM1 | PM3 | AM1 | PM3 |
| -Et | −71.6 | −71.0 | −70.4 | −69.8 | −74.7 | −71.7 | −78.6 | −75.6 |
| -Me | −71.3 | −70.8 | −70.1 | −69.5 | −74.6 | −71.5 | −78.5 | −75.4 |
| -$NH_2$ | −71.5 | −70.8 | −70.2 | −70.1 | −74.2 | −72.2 | −77.6 | −76.8 |
| -OH | −75.0 | −73.2 | −70.6 | −72.4 | −77.5 | −74.5 | −79.0 | −77.4 |
| -CHO | −109.6* | −90.5* | −83.1 | −90.8* | −110.7* | −93.8* | −115.0* | −96.5* |
| -CN | −109.0* | −93.7* | −83.6 | −93.2* | −110.2* | −96.2* | −115.2* | −98.9* |
| -CCH | −78.3 | −76.5 | −77.0 | −75.5 | −80.9 | −77.0 | −107.6* | −89.0* |
| -F | −75.6 | −75.1 | −74.4 | −73.8 | −80.5 | −78.4 | −82.1 | −81.0 |
| -SH | −79.5 | −79.3 | −78.4 | −78.4 | −81.9 | −79.2 | −108.3* | −91.9* |

* The C-N bond lengths between the ring N atom and the carbonyl C atom for these labeled complexes are longer than 2.7 Å implying complete acylation. For other unlabeled complexes, they are 1.58-1.69 Å implying stable tetrahedral intermediate complexes.

**Table 4.** DSE (difference in stabilization energy, kcal/mol) Values for the C1-substituent Effects of the Substituted *N*-vinyl-2-amino β-lactams

| | DSE($CH_3$-H) | | DSE(OH-H) | | DSE(SH-H) | |
|---|---|---|---|---|---|---|
| | AM1 | PM3 | AM1 | PM3 | AM1 | PM3 |
| -Et | 1.2 | 1.2 | −3.1 | −0.7 | −7.0 | −4.6 |
| -Me | 1.2 | 1.3 | −3.3 | −0.7 | −7.2 | −4.6 |
| -$NH_2$ | 1.3 | 0.7 | −2.7 | −1.4 | −6.1 | −6.0 |
| -OH | 4.4 | 0.8 | −2.5 | −1.3 | −4.0 | −4.2 |
| -CHO | 26.5 | −0.3 | −1.1 | −3.3 | −5.4 | −6.0 |
| -CN | 25.4 | 0.5 | −1.2 | −2.5 | −6.2 | −5.2 |
| -CCH | 1.3 | 1.0 | −2.6 | −0.5 | −29.3 | −12.5 |
| -F | 1.2 | 1.3 | −4.9 | −3.3 | −6.5 | −6.5 |
| -SH | 1.1 | 0.9 | −2.4 | 0.1 | −28.8 | −12.6 |

not so negative because of π-donating properties. All these trends are what one might expect for β-lactams, but the present study adds quantitative correlations to the qualitative argument.

In order to facilitate the comparison of substituent effect at the C1 position (*X* in Figure 2), difference of stabilization energy(DSE) is calculated for a given *R* group using the *X*=*H* case as the reference. DSEs are listed in Table 4. DSEs for the -$CH_3$ group are all positive implying that the methyl substituted β-lactams are less reactive. By the same token, -OH substituted one is slightly more reactive and the -SH substituted one is most reactive. DSE values in Table 4 suggest that the activity of 3-cephem compounds will be best when the *S* atom is connected to the C1 position provided that the activity follows reactivity. In this vein, not so much activity is expected for the O connected 3-cephems. These trends are in line with the known activities. DSEs are conspicuously larger for -CHO and -CN groups for the -$CH_3$ connected to the C1 position in AM1 calculation. Since PM3 does not show the same effect, it might be an artifact of AM1 method. On the other hand, DSEs are large negative values in both methods for -CCH (−29.3 kcal/mol for AM1 and −12.5 kcal/mol for PM3) and -SH (−28.8 kcal/mol for AM1 and −12.6 kcal/mol for PM3) when the S atom is connected to the C1 position.

In conclusion, *N*-vinyl-2-amino β-lactams become more reactive when the sulphur atom is connected to the C1 position and strong π-acceptors are attached to the *N*-vinyl terminal. Calculated reactivities are what one might expect from the reaction mechanism of acylation caused by nucleophilic attack and also from the antibiotic activities of cephalosporins. Once this correlation between calculated reactivity and the measured activity for any lead compound can be established in the near future, quantum chemical calculations can be utilized in the prescreening of what should be experimentally examined. Additional studies involving more realistic compounds will be performed.

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