Chem., **6**, 165 (1977); (c) J. Suh and I. M. Klotz, *J. Polymer. Sci. Pol. Chem. Ed.*, **16**, 1943 (1978); (d) J. Suh and I. M. Klotz, *J. Am. Chem. Soc.*, **106**, 2373 (1984).

3. D. C. Sherrington, "Polymer-supported Reactions in Organic Synthesis", P. Hodge and D. C. Sherrington, Eds., Wiley, New York, (1980), Chapter 3.

4. J. Suh and Y. H. Yoon, *Bull. Korean Chem. Soc.*, **6**, 249 (1985).

5. Dowex anion-exchange resins were purchased from Sigma Chemical Co. The sodium salt of A⁻ was obtained by reacting A with sodium ethoxide, and the yield and product

distribution for ethylation of A⁻ with EtBr conducted under various conditions were measured by ^{1}H nmr and gas chromatography as reported previously.[4] The progress of ethylation was checked daily for up to 5-7 days, and it was found that the maximum yield was attained within 3 days. The yield and product distributions were not affected significantly by the speed of stirring of the reaction mixture.

6. E. V. Dehmlow and S. S. Dehmlow, "Phase Transfer Catalysis", 2nd Ed., Verlag-Chemie, Weinheim (1983), p. 144.

Computer Graphics / Molecular Mechanics Studies on Non-Classical β-Lactam Structures*

Sung Kee Chung

Department of Chemistry, Pohang Institute of Science & Technology, Pohang 790-600

In the preceding paper[1] we described calculation of geometries of several representative β-lactam antibiotics by computer graphics and molecular mechanics (CG/MM) energy minimization, and found reasonable agreements between the calculated geometries and the X-ray crystal structures. The discrepancies in the compared geometries between the calculated and the X-ray structures were attributed to the crystal packing effects. It was concluded that the CG/MM energy minimization procedures based on the MM-2 and AMBER force fields could generate reasonable β-lactam geometries, especially in terms of the molecular parameters considered to be critical for the biological activities, *e.g.*, the pyramidal character of the amide nitrogen and the Cohen distance.[2]

In the recent years there have been a number of attempts to design non-classical β-lactams or their structural analogs.[3-14] Therefore, it seemed very interesting to examine the possibility of predicting the critical molecular parameters of some of these and other hypothetical compounds by using the CG/MM method. Thus, we have selected a number of novel β-lactam analogs, *i.e.* compounds **1-8**, and produced calculated structures by the procedures previously described.[1] The characteristic molecular parameters of the calculated geometries of compounds **1** through **8** are listed in Table 1.

The γ-lactam **1** was reported in the patent literature to have antibacterial activities.[3] The calculated molecular structure of **1** shows a substantial degree of pyramidal character (335.6 and 306.0 °C) and a reasonable Cohen distance (3.485 and 3.384 A), thus meeting the minimum structural requirements for biological activity. Baldwin, *et al.* synthesized the phenoxyacetyl derivative of the γ-lactam **3**, and found it to have no antibiotic activity. The X-ray crystallographic studies of the corresponding *t*-butyl ester showed the sum of the

Table 1. Molecular Parameters for "Non-classical β-Lactams"

Compound	Bond angle around N (Deg)		Cohen Distance (A)*	
	MM-2	AMBER	MM-2	AMBER
1	335.6	306.0	3.485	3.384
2	341.9	327.5	3.112	3.080
3	341.1	325.0	3.967	4.001
4	355.7	344.2	3.098	2.887
5	357.6	352.8	3.441	3.439
6	357.6	354.0	3.115	3.030
7	360.0	356.7	2.995	2.789
8	360.0	356.5	2.980	2.784

*Distance between the oxygen atom of the β-lactam amide functionality and the carbon atom of the carboxy group.

angles around nitrogen was 326° and the Cohen distance 4.1 A.[4,5] The calculated structure of compound **3** also indicated a pyramidal lactam nitrogen (341.1 and 325.0°) and the Cohen distance being a bit too long (3.967 and 4.001 A) to show the bioactivity. Based on the calculated molecular parameters, however, the epimeric structure **2** may be predicted to have a more desirable Cohen distance (3.112 and 3.080 A), and therefore to possess some biological activities.

Synthesis of the phenoxyacetyl derivative of compound **4** was reported to show "weak but real" antibacterial activity against both gram positive and gram negative bacteria.[6] The calculated geometry indicates a low degree of pyramidality (355.7 and 344.2°) and a low limit number (3.098 and 2.887 A) of the desirable Cohen distance range (3.0-3.9 A). The phenoxyacetyl derivative of structure **5** was reported to have a planar amide nitrogen and no antibacterial activity.[7,8] The calculations show a reasonable Cohen distance (3.441 and 3.439 A), but a virtually planar geometry around the amide nitrogen (357.6 and 352.8°) in accord with the experimental
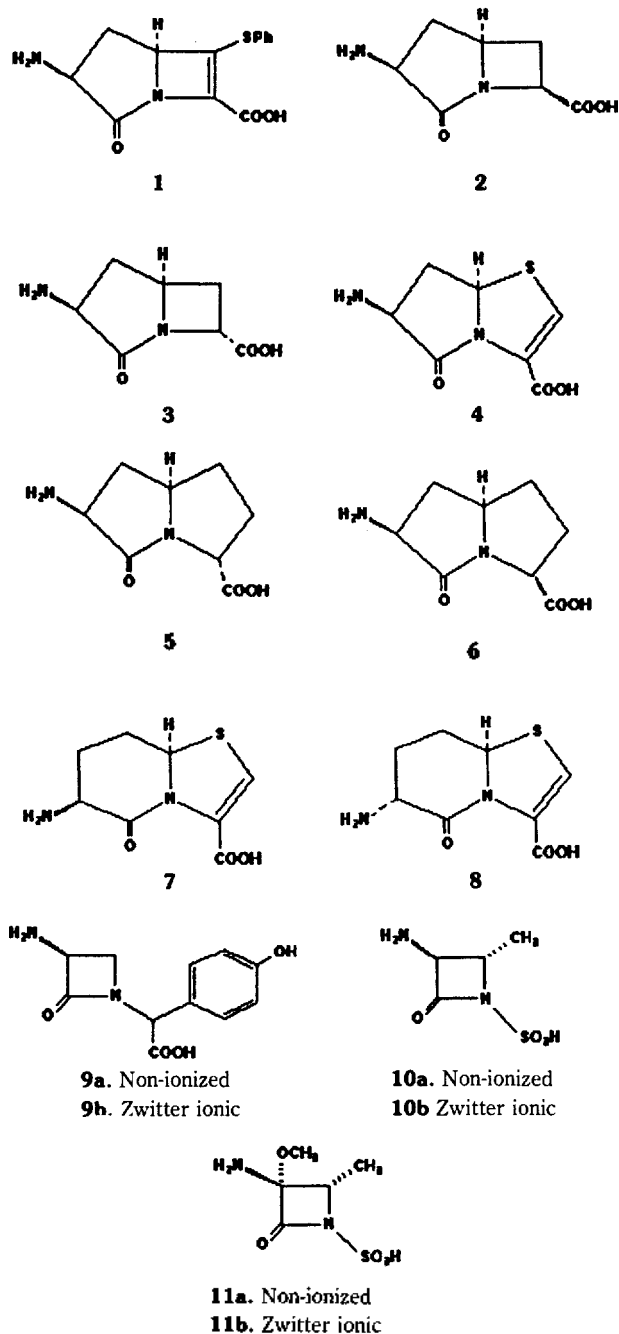
Communications to the Editor

Bull. Korean Chem. Soc., Vol. 10, No. 2, 1989 217

Table 2. Molecular Parameters for Monobactams

Compound	Bond angle around N (Deg)		Cohen Distance (A)[a]		Diatance (A)[b] NH-CO$_2$H	
	MM-2	AMBER	MM-2	AMBER	MM-2	AMBER
9a	355	352	3.099	3.009	5.400	5.220
9b	349.5	337.4	3.695	3.461	5.397	5.099
10a	359.9	—	3.225	—	4.607	—
10b	329.0	—	3.285	—	3.513	—
11a	359.6	—	3.217	—	4.600	—
11b	329.6	—	3.271	—	3.510	—

[a]Distance between the oxygen atom of the β -lactam amide functionality and the carbon (sulfur) atom of the carboxy (sulfonate) group.
[b]Distance between the 3-amino group and the carbon (sulfur) atom of the carboxy (sulfonate) group.

1

2

3

4

5

6

7

8

9a. Non-ionized
9h. Zwitter ionic

10a. Non-ionized
10b Zwitter ionic

11a. Non-ionized
11b. Zwitter ionic

observations. The calculated structure of epimer **6** also indicates a virtually planar amide nitrogen and, therefore, predicts no bioactivity.

Very recently, synthesis of compound **7** was reported without any data on the biological activities.[9] The calculations would suggest a marginal or no antibacterial activity for this compound (**7**) and its epimer (**8**), since both of them are expected to have planar amide nitrogens and the Cohen distances that are outside the required range.

The discovery of biologically active monobactams has presented a significant exception to the definition of the structural requirements for the antimicrobial activity of β -lactams.[15] The X-ray crystallographic studies on several monobactams have indicated no steric activation in these cases as opposed to the bicyclic β -lactams, since the azetidinone amide nitrogens are planar.[16,17] It was proposed that the electron withdrawing effect by the sulfonate residue might provide the necessary chemical activation of the β -lactam ring in sulfazecin and its derivatives.[15] However, a similar activation mechanism is absent in nocardicins, another class of monobactam antibiotics.

We have previously discussed, on the basis of the geometry calculations, a possibility that the amide nitrogen in monobactams may take up a pyramidal geometry in the bioactive conformations.[1] We have now carried out the geometry calculations on additional monobactam structures such as **9-11** in order to further explore our proposal. The important molecular parameters for these structures are shown in Table 2.

It is interesting to note several observations in these results. First, the nocardicin type structure (**9**) shows a considerable degree of pyramidality. Secondly, a substantial degree of pyramidality is induced by the electrostatic interactions between the amino and the sulfonate functionalties in the zwitter ionic structures (**10b** and **11b**) compared with the non-ionic structures (**10a** and **11a**). This observation supports the proposed idea that the pyramidal geometry may easily be induced through the electrostatic and other binding interactions between monobactam antibiotics and the active residues of the enzyme. Thirdly, the methoxy substituent at the 3-position appears to have little effect on the geometry of the antibiotics, but it has been found to decrease the total conformation energies by ca. 50 KJ through electrostatic stabilizations despite the increased van der Waals energy (**10a**-120.95; **10b**-84.34; **11a**-70.14; **11b**-33.53 KJ/mole). Our efforts in the design of novel molecular structures with bioactivities similar to those of β-lactam antibiotics are continuing.

References

1. S. K. Chung and D. F. Chodosh, *Bull. Kor. Chem. Soc.*, **10**, 185 (1989).
2. N. C. Cohen, *J. Med. Chem.*, **26**, 259 (1983).
3. J. V. Heck, US Patent 4,428,960, Jan. 31, 1984.
4. J. E. Baldwin, R. M. Adlington, R. H. Jones, C. J. Schofield, C. Zaracostas and C. Greengrass, *Tetrahedron*, **42**, 4879 (1986).
5. *idem.*, *J. Chem. Soc. Chem. Comm.*, **1985**, 194.
6. J. E. Baldwin, C. Lowe, C. Schofield and E. Lee, *Tetra-*

hedron Lett., **1986,** 3461 and 5042.

7. J. E. Baldwin, M. F. Chan, G. Gallacher, M. Otsuka, P. Monk and K. Prout, *Tetrahedron,* **40,** 4513 (1984).

8. *idem., J. Chem. Soc. Chem. Comm.,* **1983,** 250.

9. E. Lee, *Proc. 7th Symp. Org. Chem.,* April 1988, KRICT, Kor. Chem. Soc. Compound **7** was recently bound to have no bioactivity-personal communication with professor E. Lee.

10. J. G. Gleason, T. F. Buckley, K. G. Holden, D. B. Bryan and P. Siler, *J. Am. Chem. Soc.,* **101,** 4730 (1979).

11. C. L. Branch and M. J. Pearson, *Tetrahedron Lett.,* **1982,** 3003.

12. J. M. Indelicato and C. E. Pasini, *J. Med. Chem.,* **31,** 1227 (1988).

13. D. Agathocleus, S. Buckwell, P. Proctor and M. I. Page, "Recent Advances in the Chemistry of β-Lactam Anti-

biotics", S. M. Roberts and A. G. Brown, Eds., The Royal Society of Chemistry, Burlington House, London, 1985, p. 209.

14. G. Lowe and S. Swain, in *ibid.,* p. 209.

15. W. H. Koster, C. M. Cimarusti and R. B. Sykes, "Chemistry and Biology of β-Lactam Antibiotics", R. B. Morin and M. Gorman, Eds., vol. 3, Academic Press, New York, NY, 1982.

16. R. B. Sykes, C. M. Cimarusti, D. P. Bonner, D. M. Floyd, N. H. Georgopapadakou, W. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. L. Rathnum, W. A. Slusarchyk, W. H. Trejo and J. S. Wells, *Nature,* **291,** 489 (1981).

17. K. Kamiya, M. Takamoto, Y. Wada and M. Asai, *Acata Crystal., Sect. B.,* **B37,** 1626 (1981).

A New Procedure for β-Alkoxycarbonylation and β-Acylation of Enones

Sunggak Kim*, Phil Ho Lee, and Sung Soo Kim

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 130-012.

Received January 19, 1989

The generation of specific enolates via Michael addition of nucleophiles to α,β-unsaturated ketones has proven to be an extremely useful process for functionalization of enones.[1-5] In this regard, we have recently reported that ylides derived from enones via phosphoniosilylation serve effectively as enone β-anion equivalents to give 2,3-unsaturated-1,6-dicarbonyl and β-hydroxyalkylated compounds in high yields.[6] On the basis of these results, it has been studied the possibility of β-alkoxycarbonylation and β-acylation of enones. Moreover, there are no general methods for the synthesis of 2,3-unsaturated-1,4-dicarbonyl compounds[7] which is important in organic synthesis.[8] Therefore, we have examined the reaction of ylides (2) derived from phosphonium salt silyl enol ether (1) with alkyl chloroformates and acid halides, as shown in Scheme I.

Alkoxycarbonylation of enones at β-position was achieved by the reaction of ylide (2) with benzyl chloroformate or ethyl chloroformate followed by the elimination of triphenylphosphine with tetrabutylammonium fluoride to obtain 2,3-unsaturated-1,4-dicarbonyl compounds in good yields by one-pot procedure. In order to obtain β-acylated, β-enones, acid chlorides such as benzoyl chloride and acetyl chloride were used as an electrophile but gave poor results under the present conditions. Thus, the reaction of ylide (2) with benzoyl chloride and acetyl chloride gave β-benzoyl-and β-acetyl-2-cyclohexen-1-one in 13% and 10% yield, respectively along with predominantly several unidentified byproducts. However, the reaction of this Wittig reagent with benzoyl fluoride instead of benzoyl chloride proceeded rapidly and much more cleanly, yielding β-benzoylated 2-cyclohexene-1-one in 65% yield. In the case of the β-benzoylation of carvone, the yield was improved by the use of tributylphos-
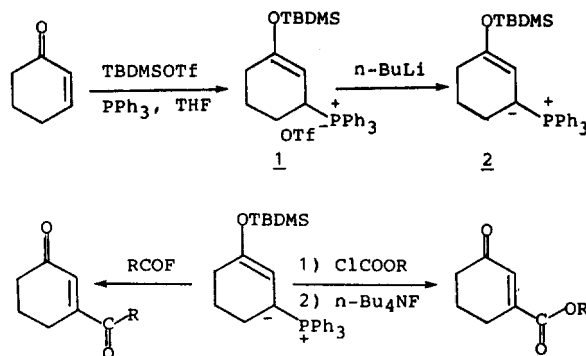
Scheme 1

phine instead of triphenylphosphine. This result is probably due to more reactive ylide of tributylphosphine than that of triphenylphosphine. Some experimental results are given in Table 1 and illustrate the efficiency and applicability of the present method. Especially, it is noteworthy that this overall conversions can be accomplished by one-pot procedure from α β-unsaturated ketonones without any isolation of the intermediates.

The typical procedure for β-benzyloxycarbonylation of enones is as follows. To a solution of triphenylphosphine (231 mg, 0.9 mmol) in tetrahydrofuran (4 mℓ) were added 2-cyclohexen-1-one (85 mg, 0.9 mmol) and TBDMSOTf (244 mg, 0.9 mmol) at -30 °C. After being stirred at room temperature for 30 min, the reaction mixture was cooled to -78 °C and n-butyllithium (0.6 mℓ, 1.0 mmol) was added dropwise to give a black-colored ylide solution. The reaction mixture was stirred for 30 min at -78 °C and benzyl chloroformate (165 mg, 1.0 mmol) was added to the ylide solution. After being warm-