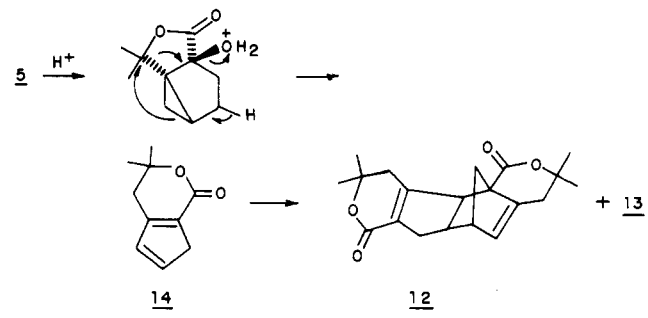
to the bicyclo[3.1.0]hexane system **9** and *o*-menthane skeleton **10** is concerned.

A first attempt to transform **5** into lactone **11**, an *o*-menthane isolated from the urine of koala bear,[7] treating **5** with perchloric acid, led to the formation of two dimers **12** (36%) and **13** (18%). Spectroscopic data[8] and X-ray diffraction[5] revealed structure **12** for the major product, indicating that a Diels-Alder cycloaddition had occurred between two diene molecules possessing structure **14**. We are currently investigating the application of these rearrangement compounds in natural product synthesis.



(7) Southwell, I. A. *Tetrahedron Lett.* **1975**, 1885.

(8) Spectral data of **12**: mp 162.6–163.6 °C; IR ν_{max}^{KBr} (cm^{-1}) 1720 (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 1.31, 1.36, 1.46 and 1.52 (4 s, 3 H each), 1.95 (d, 2 H), 3.18 (m, 2 H), 3.93 (dm, J = 9.2 Hz, 1 H), 5.80 (m, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.6 (s), 163.5 (s), 153.6 (s), 140.2 (s), 131.0 (s), 128.7 (d), 82.2 (s), 80.9 (s), 64.2 (d), 56.3 (t), 55.7 (s), 46.6 (d), 42.0 (d), 37.9 (t), 37.1 (t), 32.2 (t), 29.7 (q), 29.5 (q), 27.5 (q), 27.1 (q).

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Registry No. 1, 18172-67-3; 2, 471-83-0; 3, 38651-65-9; 4, 123482-50-8; 5, 123380-83-6; 6, 123380-84-7; 12, 123380-85-8.

A New MODEL Parameter Set for β-Lactams

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Summary: The original parameters in the MM-2 force field of MODEL gave poor structural data for β-lactams. A new atom type was defined for the β-lactam nitrogen, and new parameters, giving substantially better minimized structures, were derived using X-ray and AMPAC data.

Sir: β-Lactams have long been of interest to scientists because of their antibiotic activity.[1] In particular, it is known that their antibacterial activity, on a molecular level, involves inhibition of the transpeptidase normally responsible for cross-linking proteins in the formation of bacterial cell walls.[2] A thorough understanding of this process necessitates good structural information about the β-lactam in question. We undertook a structural study of these materials using molecular mechanics calculations and found that the predicted geometries of these molecules differed substantially from experimentally determined geometries. Other workers have obtained similar poor results for penicillin analogues and developed new modeling parameters to overcome their difficulties.[3] Using X-ray data[4,5] and semiempirical calculations (AMPAC),[6] we have developed a new set of parameters for β-lactams that provides much better structural information than the original parameters in the MM-2/MODEL force field.[7,8]

Results

As an initial test case, we examined the geometry of **1** using the MM-2 force field available in MODEL.[9] Overlay of the calculated geometry with the X-ray structure showed a root mean square (rms) deviation of 0.092 Å when the seven ring atoms were compared. While this degree of deviation initially appeared satisfactory, detailed examination of the differences between the two structures indicated that there were substantial errors in the calculated bond lengths and angles around the β-lactam nitrogen. We found that the sum of the angles around the β-lactam nitrogen in the calculated structure differed from the X-ray structure by as much as 30°. Since this sum has been used as an indicator of activity, this was particularly disturbing.[10,11] Realizng that the character of the nitrogen in the β-lactam might best be viewed as having an intermediate hybridization (i.e., ~$sp^{2.5}$), we decided to examine the geometry of the β-lactam using a transition state type nitrogen (atom type 55) already parameterized in the MODEL force field. Use of this atom type in the structure minimization gave improved results in the bond lengths but poorer overall results with an rms deviation of 0.110 Å in the ring atoms. In particular, while the X-ray structure showed the four-membered ring to be almost completely planar, there was a substantial degree of puckering of this ring in the calculated structure. This lack of planarity introduced a significant degree of error in all of the bond angles. It was evident that the available parameters were inappropriate for the purpose of predicting β-lactam structures.

In our development of new parameters, we defined a new atom type for the β-lactam nitrogen. In many molecular mechanics programs, there is an option to specify new atoms as wild card types for which parameters are easily

(1) *β-Lactam Antibiotics*; Salton, M. R. J., Shockman, G. D., Eds.; Academic Press: New York, 1981.

(2) Knowles, J. *Acc. Chem. Res.* **1985**, *18*, 97.

(3) Wolfe, S.; Khalil, M.; Weaver, D. F. *Can. J. Chem.* **1988**, *66*, 2715.

(4) Allen, F. H.; et al. *Acta. Crystallogr. B.* **1979**, *35*, 2331.

(5) We wish to thank Drs. Dennis Keith and Kin-Chun Luk of Hoffman-LaRoche for providing us with X-ray coordinates for five of our structures.

(6) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(7) These new parameters are currently being incorporated into MODEL and will be available in newer versions of the program.

(8) The difficulties we found in the MODEL treatment of β-lactams were unrelated to the now resolved problems of MODEL treatment of any four-membered ring.

(9) All molecular modeling calculations were done on version 2.94 of MODEL developed by K. Steliou and W. C. Still. This program is available from Kosta Steliou at the University of Montreal. We wish to thank Kosta Stelio for his helpful comments in the preparation of this manuscript.

(10) Baldwin, J. E.; Greengrass, C. W.; et al. *Tetrahedron* **1986**, *42*, 4879

(11) Woodward, R. B. *Philos. Trans. R. Soc. London, Ser. B* **1980**, 239.

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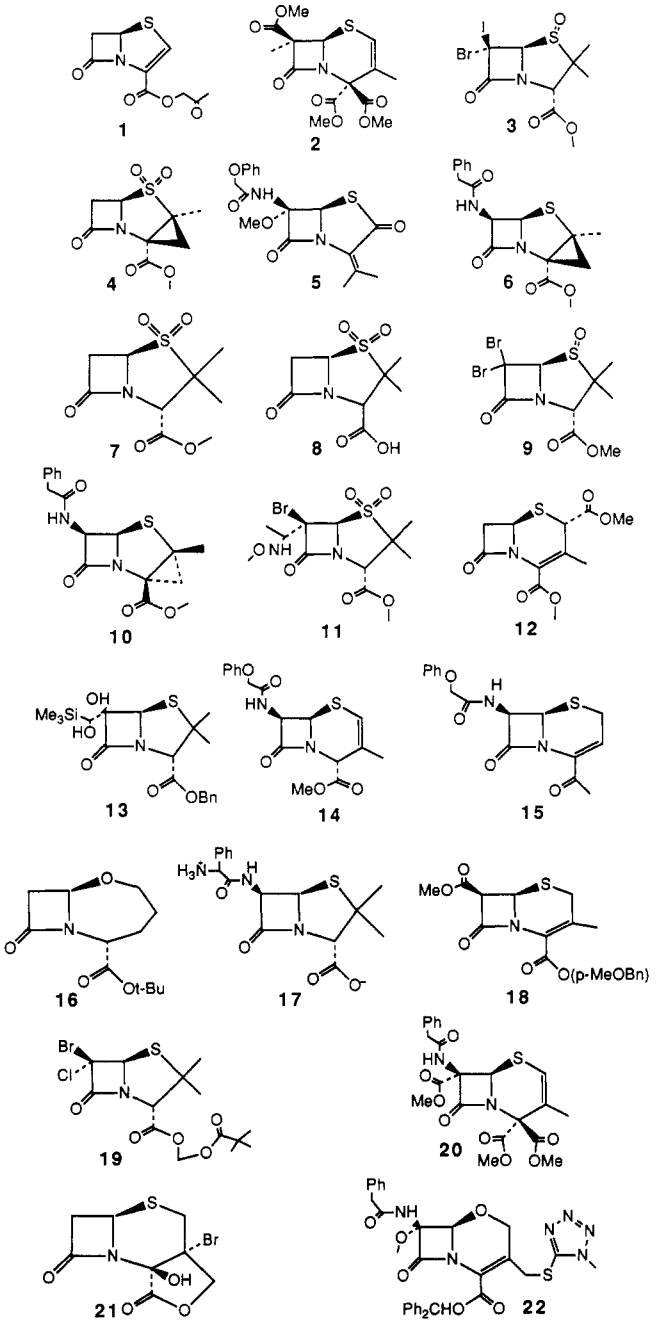

Figure 1. β-Lactams for X-ray study.

adjusted. In MODEL, we chose the wild atom type 60 with the symbol Z2. Our starting parameters were those already defined for the transition-state nitrogen, replacing atom 60 for atom 55. The approach we took to the parameter development was empirical, depending primarily on comparisons of the calculated structure with X-ray data. Noting the difficulty with ring puckering, we adjusted a number of torsional parameters involving the lactam ring atoms so as to increase the relative stabilities of eclipsed conformations. In most cases, this involved using negative V_3 values. The stabilization of the eclipsed conformations in this manner would tend to favor a planar ring where all dihedral angles internal to the ring are zero.[12]

Further adjustments were made to the bonds lengths and angles. The natural bond lengths were set to reflect the actual values found in the X-ray structures and force

(12) Allinger, N. L.; Burkert, U. *Molecular Mechanics*, ACS Monograph 177, 1982.

Table I. Calculated and Experimental Bond Angles for β-Lactams

structure	rms dev, Å	angle, deg a	b	c	d	e[a,b]
1	0.058	109.0	88.2	91.3	111.7	128.0
		105.4	90.0	91.6	113.3	126.6
2	0.075	105.8	99.8	95.8	127.8	136.3
		109.9	98.2	92.9	129.3	137.7
3	0.054	105.6	89.8	92.7	116.9	124.9
		102.5	89.4	95.6	119.1	128.2
4	0.094	103.5	97.6	92.5	117.9	130.0
	(0.071)[c]	101.5	96.0	93.1	118.3	130.5
5	0.065	105.0	91.9	91.6	113.3	127.7
		106.8	92.3	95.2	117.0	126.4
6	0.086	106.0	92.2	92.8	115.0	131.1
		106.1	93.2	93.2	115.9	127.0
7	0.035	101.9	92.0	92.6	119.7	126.3
	(0.036)	101.3	94.2	92.5	119.7	125.2
8	0.054	102.1	91.8	92.6	119.7	126.3
	(0.055)	99.3	93.2	92.5	119.1	127.5
9	0.089	105.3	89.8	93.0	117.1	125.2
		99.7	89.1	95.3	117.6	129.1
10	0.099	104.9	92.5	92.1	115.6	131.3
		104.6	91.6	92.2	114.1	129.7
11	0.051	98.2	92.4	93.7	122.0	129.2
	(0.055)	103.1	93.1	95.5	117.0	128.0
12	0.048	112.2	94.5	92.5	125.3	132.8
		109.4	95.1	94.3	125.2	134.3
13	0.041	105.3	93.9	93.4	117.7	128.7
		106.7	94.5	95.8	116.5	126.2
14	0.068	107.8	97.9	95.4	127.7	136.0
		110.5	97.2	95.7	127.2	136.4
15	0.069	110.8	93.9	92.9	125.6	134.9
		109.4	92.1	95.1	124.9	132.6
16	0.053	114.0	112.7	94.4	129.4	133.1
		113.0	112.9	96.4	131.0	132.4
17	0.023	103.0	89.7	92.5	119.0	125.5
		103.8	90.4	93.7	118.0	126.1
18	0.071	110.4	94.5	93.2	125.7	133.7
		108.0	95.3	89.7	126.7	131.8
19	0.044	103.9	95.0	95.4	118.7	128.7
		105.6	95.3	95.4	116.0	130.7
20	0.086	106.7	98.3	94.8	128.8	135.7
		109.7	97.8	96.7	126.6	136.6
21	0.072	105.8	96.0	95.0	128.0	136.6
		110.4	96.2	93.3	127.6	138.2
22	0.093	113.2	109.7	90.7	119.1	129.6
		109.6	108.9	94.6	119.7	138.0

[a] Bond angle definition in Figure 2. [b] Experimental angles (X-ray) appear below calculated angles in each entry. [c] RMS deviations for sulfone β-lactams calculated using AMPAC-derived parameters are in parentheses.

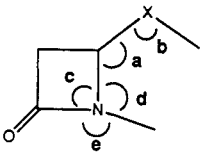

Figure 2. Bond angle definition for Table I.

constants to reflect the compressibility of the bonds. The same approach was used in the development of the corresponding values for the bond angles. The adjustments were followed by minimization of the β-lactam geometries using the newly derived parameters. These parameters were evaluated by comparison of calculated and X-ray data on twenty-two structurally diverse β-lactams. Adjustments to the parameters were made iteratively until the calculated stuctures gave satisfactory agreement with the X-ray data, in terms of ring atom overlay and selected bond length and angle parameters. The results of our study are shown in Table I.

Our experience has shown that torsional data derived from AMPAC generally correlate well with MODEL data.[13]

Thus, it appeared that data from AMPAC might be useful in refining our newly developed parameters. We compared dihedral driver data from AMPAC and MODEL for a series of simple substituted β-lactams, using our new MODEL β-lactam parameters. Only in the case of the sulfone substituent were there any major discrepancies. It is our belief that the AMPAC data was not to be completely trusted in the sulfone case, as it is known that hypervalent sulfur compounds are not well described in the AM1 Hamiltonian.[14,15]

We experimented with numerous parameter sets in an attempt to match the AMPAC data, and found that any MODEL parameter set that would reproduce the AMPAC data gave poor structural data for the sulfone β-lactams. In the course of this effort, however, we did derive an additional parameter set that gave good structural data unrelated to the AMPAC information. These additional parameters are completely different from those derived from X-ray data, yet they give as good or better structural results. It is unclear at this time which of the new parameter sets is best for sulfone β-lactams. The limited number of structures does not as yet allow for this distinction. With more data, one set may well emerge as superior.

(13) Dihedral driver calculations involve using AMPAC to locate the global minimum. All structural features are then held constant at the calculated minimum-energy values except for the relevant dihedral angles. These are rotated through 360° with 10° increments, giving the torsional barrier to rotation. This approximates the rigid rotor option available in MODEL. We compared the data from these two sources and found remarkable agreement for a variety of systems including β-lactams, formamides, and alkanes. It is likely that AMPAC data can be used to derive MODEL parameters by adjusting these parameters to give a MODEL torsional curve matching the AMPAC curve.

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Conclusions

The need for easily accessed, useful structural data prompted us to use molecular mechanics calculations. Recognition that the original parameters were poor led to our development of these new parameters. We believe the new parameters are useful in giving accurate structural data for β-lactams. Although force field calculations have certain weaknesses, the ease of the development of new parameters is a major asset and adds greatly to the utility of these techniques.

Supplementary Material Available: Tables containing MM-2 atom types, X-ray and MODEL data for selected β-lactams, and X-ray and AMPAC derived parameters for MM-2 calculations on β-lactams (7 pages). Ordering information is given on any current masthead page.

Samarium(II) Iodide Mediated Carbocycles from Carbohydrates: Application to the Synthesis of the C Ring of Anguidine

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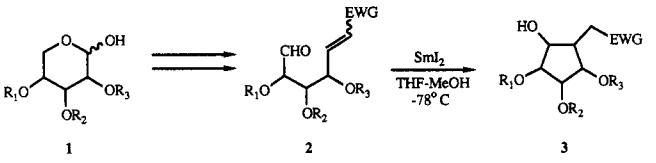
Summary: The enantioselective synthesis of the C ring of anguidine in protected form has been achieved from the known protected (L)-arabinose lactol **7**. A key transformation in this route involved the diastereoselective samarium diiodide mediated cyclization of carbohydrate template **11** to the highly oxygenated carbocycle **12**. The stereochemistry of this cyclization was confirmed by a combination of chemical transformations and nuclear Overhauser effect studies.

Sir: Recently, there has been considerable interest in the transformation of carbohydrates to carbocycles.[1] Most current technology involves a free-radical approach in which tributyltin hydride mediates a well-known 5-hexenyl-type of radical cyclization from a bromide, iodide, or thiocarbonyl imidazole precursor.[2] We have examined a different methodology which also directly addresses this synthetic problem; however, it differs in that it utilizes the one-electron reducing agent, samarium diiodide,[3] to couple

Scheme I



two sp^2-hybridized carbon centers in a modified carbohydrate template to construct a polyoxygenated cyclopentane ring, shown in Scheme I.[4] In this paper, we detail the first application of this methodology to an efficient enantioselective construction of the highly oxygenated C ring of anguidine.

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(2) For a review of these processes see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: New York, 1986. (b) Curran, D. P. *Synthesis* **1988**, *417*, 489. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Neumann, W. P. *Synthesis* **1987**, 665.

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