($CDCl_3$) δ 170.2, 170.0 (OCO), 138.3, 137.3, 137.2 (aromatics ipso), 128.4-127.7 (aromatics), 78.7-66.2 (C-1-C-6, CH_2O), 21.0, 20.7, 20.7 (3 CH_3CO).

1-*O*-Benzoyl-*myo*-inositol (13): white solid; mp 84-87 °C (hexane-methanol); ^1H NMR (DMSO-d_6 + D_2O) δ 8.03-7.51 (m, 5 H, aromatics), 4.65 (dd, 1 H, J = 2.6 Hz, J = 10.3 Hz, H-1), 3.93 (br s, H-2), 3.73 (t, 1 H), 3.43 (t, 1 H, J = 9.3 Hz), 3.26 (dd, 1 H, J = 2.4 Hz, J = 9.5 Hz, H-3), 3.06 (t, 1 H, J = 9.0 Hz); ^{13}C NMR (DMSO-d_6) δ 165.6 (OCO), 133.0, 130.3, 129.4, 128.4 (aromatics), 75.5, 75.1, 72.3, 72.2, 71.3, 71.2, 70.1 (C-1-C-6).

1-*O*-(*p*-Methoxybenzoyl)-*myo*-inositol (14): white solid; mp 185-187 °C (methanol); ^1H NMR (DMSO-d_6 + D_2O) δ 7.95 (d, 2 H, J_{ortho} = 8.9 Hz, aromatics), 7.01 (d, 2 H, J_{ortho} = 8.9 Hz, aromatics), 4.59 (dd, 1 H, J = 2.7 Hz, J = 10.1 Hz, H-1), 3.90 (t, 1 H, J = 2.6 Hz, H-2), 3.80 (s, 3 H, CH_3O), 3.71 (t, 1 H), 3.41 (t, 1 H, J = 9.5 Hz), 3.24 (dd, 1 H, J = 2.6 Hz, J = 9.8 Hz, H-3) 3.04 (t, 1 H, J = 9.1 Hz); ^{13}C NMR (DMSO-d_6 + D_2O) δ 165.3 (OCO), 162.9 (para aromatics), 131.5 (ortho aromatics), 122.6 (meta aromatics), 113.7 (ipso aromatics), 75.1, 72.3, 71.4, 70.1, 70.0 (C-1-C-6), 55.5 (CH_3O). Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77. Found: C, 53.73; H, 5.51.

Acknowledgment. We thank the Dirección General de Investigación Científica y Técnica (Grant PB 87-0367) and Europharma S.A. for financial support and M. Isabel Jiménez Vacas (Department of Analysis) for the assistance in the GLC analysis. One of us (A.Z.) thanks the Ministerio de Educación y Ciencia for a fellowship.

Registry No. 1, 87-89-8; 2, 130296-29-6; 3, 55410-80-5; 4, 130296-30-9; 5, 130404-33-0; 6, 23486-90-0; 7, 92217-63-5; 8, 130296-31-0; 9, 16749-97-6; 10, 130404-34-1; 11, 130404-35-2; 12, 115184-71-9; 13, 130296-32-1; 14, 130296-33-2.

3-*exo*-Methylenecephalosporins: Structure and Thermodynamics by Experiment and Theory

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Received May 17, 1990

Although X-ray crystal structures of cephalosporins[1] **1** and their Δ2 isomers[2] **2** have been reported, little is known of the details of the structure of the 3-*exo*-methylene isomer **3**, with the exception of its stereochemistry.[3] From a thermodynamic standpoint, it is known that **1** and **2** are nearly isoenergetic. For example, when R_1 is hydrogen, the isomer ratio of **1**:**2** is about 3:7 at equilibrium, but when R_1 is larger, the ratio is about 7:3.[4] This dearth of structural and thermodynamic information is surprising

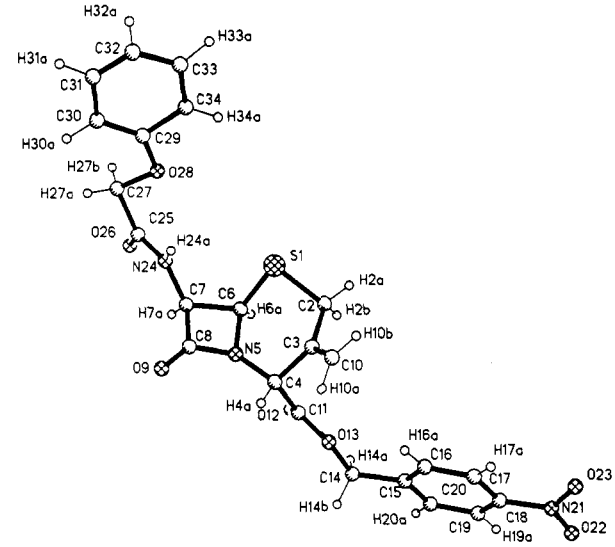


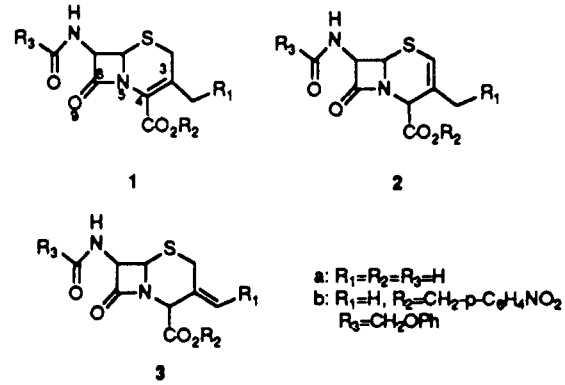
Figure 1.

Table I. Key Structural Features of Cephalosporin Isomers from X-ray Crystallography[a]

	1[b]	2[c]	3b[d]
C8-O9	1.223 (0.065)	1.216 (0.017)	1.225
N5-C8	1.396 (0.070)	1.343 (0.009)	1.347
C4-N5	1.429 (0.040)	1.430 (0.021)	1.464
C3-C4	1.340 (0.035)	1.539 (0.017)	1.551
N height[e]	0.18 (0.062)	0.04 (0.026)	0.02

[a] Distances in angstroms. Values in parentheses are one standard deviation. [b] Average of data from structures ACMPXC, BODKOU, BZCMXC, CEFMEN, CEPHGLY, CEPHAP, CEPHHM, CEPHNA, CEPHNB, CETHNA, and TZACOL from Cambridge Crystallographic Database. See ref 1b. [c] Average of data from structures DMCXCM, PAMXCP, and PODACE. [d] This work. [e] Defined in text.

given the large amount of synthetic effort directed toward **3**[5] and its importance as a precursor to cephalosporins such as cefaclor which contain a heteroatom at C3 rather than a carbon atom.[6] This paper reports the first X-ray crystal structure of a 3-*exo*-methylenecepham, **3b**, calorimetric data for its isomerization to **1b**, and a comparative study of semiempirical molecular orbital methods for the study of cephalosporins and their isomers.



Results and Discussion

Compound **3b** was prepared by known procedures and was crystallized from a mixture of toluene, ethyl acetate,

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0022-3263/91/1956-0447$02.50/0

and methylene chloride. The 6-membered ring of **3b** exists in a relatively distortion-free cyclohexane chair conformation, as determined by X-ray crystallography. The length of the double bond is 1.321 (17) Å and it projects into the β face, providing a concave appearance to the molecule (see Figure 1). This orientation leaves the α face relatively accessible to attack. It was recently demonstrated that the bromination of methyl 3-*exo*-methylene-7-phthalimidocepham occurs predominantly from the α face.[7] Other key structural features are given in Table I. The shortness of the N5–C8 bond and the planarity of the lactam nitrogen (as measured by N height, the distance from this atom to the plane defined by the three atoms attached to it) are consistent with the lack of antibiotic activity in the 3-exo-methylenecephams. The sp^3 hybridization of C4 provides **2** and **3** with a significantly different relative orientation of the C4 carboxyl group than exists in **1**. It is known that this carboxyl is required for antibiotic activity, and this difference in orientation has been offered as an explanation for the lack of biological activity in the $\Delta 2$ isomers, **2**.[2a,8]

To determine the energy of 3-*exo*-methylenecepham isomers, **3**, relative to **1** and **2**, the heat of the isomerization of **3b** to **1b** was determined calorimetrically to be 4.55 kcal/mol. A solution of 0.145 mol of **3b** in methylene chloride was treated with 0.15 equiv of triethylamine at 20 °C. Under these conditions, the yield of **1b**, the kinetic product, was greater than 98% within 5 min. After the initial rapid reaction, the $\Delta 2$ isomer **2b** was produced until a mixture of **1b** and **2b** in a ratio of about 4:1 was obtained. The value of 4.55 kcal/mol is high enough to explain why isomer **3** has never been observed in equilibrated mixtures of cephalosporins and yet is low enough to not eliminate the possibility of producing **3** from **1** or **2** through selective isomerization techniques such as photochemical.

Computational analysis of the structures and energies of variously substituted azetidinones was needed for evaluation of possible mechanisms for their formation and reactions, both those involving the β-lactam ring and otherwise. The entire range of computational methods have been applied to β-lactams, including empirical conformational analysis,[9] force field methods,[10] CNDO/2,[11] semiempirical methods such as MINDO/3 and AM1,[12] and ab initio SCF molecular orbital methodology.[13] It was assumed that semiempirical methods such as MINDO/3, MNDO, or AM1 would be the highest level of theory which could provide useful estimates of the structures and energies of reactants, products, and transition states needed for prediction of chemical reactivity with a reasonable amount of computer time. Although it has been suggested that MINDO/3 is superior to the other two methods mentioned,[12] this suggestion was based on structural parameters pertaining specifically to the β-lactam amide moiety and did not evaluate the method's ability to predict relative energies. Given the added structural and thermodynamic information reported in this paper and the known inability of MINDO/3 to accurately predict the energies of 4-membered rings,[12,14] a comprehensive comparison between theoretical and experimental results on the structures and relative energies of cephalosporin isomers was performed.

Table II. Comparison of Calculated and Experimental Structural Features of Cephalosporin Isomers[a]

	MINDO/3	MNDO	AM1
fit to **1**[b]	0.160	0.142	0.140
fit to **2**	0.204	0.220	0.216
fit to **3**	0.166	0.138	0.142
N height of **1**[b]	0.06	0.20	0.27
N height of **2**	0.08	0.18	0.23
N height of **3**	0.09	0.21	0.27

[a] In angstroms. [b] Defined in text.

Table III. Relative Energies of Cephalosporin Isomers[a]

	MINDO/3	MNDO	AM1	experimental
1	0[b]	0[c]	0.7	0
2	14.5	2.5	0[d]	0.8[e]
3	19.5	9.1	4.0	4.55

[a] In kilocalories/mole. Computational results are for **1a**, **2a**, and **3a** whereas experimental results are for **1b**, **2b**, and **3b**. [b] Actual value of calculated enthalpy of formation is −181.29. [c] ΔH_f = −166.80. [d] ΔH_f = −120.04. [e] For a ratio of 4:1 for **1b**:**2b** at 23 °C.

Computational work was performed on a VAX 8800 using SYBYL[15] as an interface with the Cambridge Crystallographic Database, for visualization, preparation of MOPAC input files, and for analysis of the results. For **1**, CEPHAP (R_1 = OAc, R_2 = H, R_3 = CH_2S-4-pyridinium) was chosen as representative of those listed in Table I due to similarity of its bond lengths and angles to the average values for the entire set. The structure was pruned by removal of R_1 and R_3 and the vacancies filled with hydrogen to provide **1a** as the initial point for independent calculations using MINDO/3, MNDO, and AM1 basis sets, all with complete geometry optimization. Similarly, PODACE (**2**, R_1 = R_2 = H, R_3 = CH_2OPh) was pruned to **2a** and **3b** was pruned to **3a**. This procedure was chosen to provide initial structures for each which were biased only by crystal forces and to ensure that all molecules started with reasonable conformations, not to necessarily provide the global minimum. Since only one conformation of the dihydrothiazine ring of **1** is typically operative,[16] the only conformational space which was explored in this study was the orientation of the carboxyl group attached at C4 (rotation about the C4–CO_2R_2 bond). This was found to be a double-well potential surface with maxima in the region of coplanarity of the carboxyl function with the amide group and minima in the region of 60–70° twist. This is consistent with the X-ray structures for **1**, which, with the exception of carboxylates, all displayed twists of 40–60°. MNDO parameters were used for sulfur during the AM1 calculations since actual AM1 sulfur parameters were not available.

The extent of geometric deformation before the program achieved self-consistency (with default settings, not PRECISE) was measured by comparison of the final structures with the X-ray structures. This was performed with the FIT subroutine within SYBYL and is a least-squares minimization of the distances between the 12 pairs of atoms comprised of the eight atoms of the bicyclic ring

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system and the four non-hydrogen atoms attached to it. The results, which are shown in Table II, indicate that for structures 1 and 3 the MINDO/3 structure was significantly poorer than the MNDO or AM1 structures. As the data in Table II indicate, MINDO/3 flattened the geometry about the lactam nitrogen whereas AM1 increased the pyramidality. A comparison between calculated and experimental bond lengths for the 11 bonds which define the ring and the attached groups at positions 7 and 8 for compound 1 reveals correlation coefficients (R^2) of 0.953 for the MINDO/3 structure, 0.979 for the MNDO structure, and 0.949 for the AM1 structure, indicating a slight superiority of the MNDO method in this regard.

Key differences in the accuracy of the methods are revealed, however, in their ability to predict the relative energies of the three isomers. Table III contains the calculated relative heats of formation of these isomers and the experimentally determined relative energies. That is, the energy of the most stable isomer was set to zero and the energies of the others were adjusted accordingly within the same semiempirical method. Comparison between numbers derived from theory and experiment is possible since solvation energies of the various species are likely to be similar and little entropic differences should exist between the fairly rigid isomeric structures. These results demonstrate the clear superiority of AM1 with respect to the energetics of the isomers and the large error that is possible with MINDO/3. The availability of sulfur parameters for AM1 should provide further improvements in the reliability of this method.[17]

Conclusions

The structure of **3b**, the first 3-*exo*-methylene isomer of a cephalosporin to have its structure determined by X-ray crystallography, has been shown to be quite ordinary in terms of the length and orientation of the carbon–carbon double bond. This isomer was determined to lie 4.55 kcal/mol above its cephalosporin isomer, **1b**. Of the three common semiempirical molecular orbital methods, AM1 was found to provide the best agreement with experimentally determined relative energies of cephalosporins and their isomers and is the recommended method for analysis of these compounds, especially for analysis of possible alternate mechanisms.

Experimental Section

X-ray Crystallography. Compound **3b** crystallized in the monoclinic space group $P2_1$ with a unit cell having the dimensions a = 7.228 (4) Å, b = 10.328 (4) Å, c = 15.436 (8) Å, β = 90.415 (5)° and a calculated density of 1.39 g cm^{-3}. A total of 1747 reflections with 2θ less than 116.0° was measured on an automated four-circle diffractometer using monochromatic copper radiation. The structure was solved using the direct methods routine TREF of the SHELXTL program library and was refined by the least-squares method with anisotropic temperature factors for all atoms except hydrogen. All hydrogen atoms were included at calculated positions. The final R factor was 0.074 for 1475 unique observed reflections.

High-performance liquid chromatography (HPLC) was performed on a 25-cm Zorbax C8 column eluted at 1.25 mL/min with 55% acetonitrile and 45% aqueous buffer prepared by raising the pH of 0.3% phosphoric acid to 3 with triethylamine. Detection was by UV at 255 nm. Retention times are 9.34 min for **3b**, 10.45 min for **1b**, and 10.72 min for **2b**. Nuclear magnetic resonance spectra were obtained on a Bruker AC300 at ambient temperatures in dimethyl-d_6 sulfoxide.

***p*-Nitrobenzyl 7-(phenoxyacetamido)-3-methylenecepham-4-carboxylate (3b)** was prepared by a modification of the known reduction of the corresponding sulfoxide.[18] A methylene chloride (1000 mL) solution of *p*-nitrobenzyl 7-(phenoxyacetamido)-3-methylenecepham-4-carboxylate 1β-oxide[19] (103 g, 0.206 mol) was cooled to 0 °C and treated with acetyl bromide (31 mL, 0.309 mol) over a period of 20 min. The solution was warmed to 15 °C over the course of 1 h, and water (250 mL) was added followed by dropwise addition of 5 M NaOH solution to achieve a pH of 6. The layers were separated, and the lower layer was washed with dilute sodium chloride (500 mL). After drying over sodium sulfate, the solution was distilled at atmospheric pressure until the still temperature was 50 °C, whereupon methanol (500 mL) was added and the solution was distilled until the still temperature was 55 °C. Another 250-mL portion of methanol was added, and the slurry was cooled slowly to 0 °C. The product was collected by filtration and rinsed with methanol, and the wetcake was slurried at 80 °C for 1 h in toluene (350 mL). The slurry was cooled to ambient temperature and the product was filtered, rinsed with toluene, and dried in vacuo at 30 °C for 3 days to yield 78.4 g of **3b**. Its NMR spectra was consistent with that reported in the literature,[20] and its purity was 99% by HPLC.

The calorimetry was performed with a Mettler RC1 using a 1-L reaction vessel. Compound **3b** (70 g, 145 mmol) was dissolved in 700 mL of methylene chloride at 20 °C, and the heat capacity was measured. Triethylamine (2.2 g, 21.8 mmol) was added rapidly, and the heat load measured. The calorimeter was operated in a nonadiabatic mode, and the heat load was measured according to the following equation where ΔT_j is the differece between the temperature of the jacket fluid and the reaction mixture, ΔT_r is the change in reaction mixture temperature, and ΔT_b is the change in temperature of the base added. The adi-

$$q = UA(\Delta T_j) + mCp(\Delta T_r) + mCp(\Delta T_b)$$

abatic temperature rise was calculated by the software to be 2.1 °C, and the heat of reaction to be 4.71 kcal/mol. The process was repeated on another 70 g of **3b** at 25 °C, giving a calculated adiabatic temperature increase of 1.8 °C and a heat of reaction of 4.38 kcal/mol. The product solution when analyzed immediately by HPLC showed near quantitative conversion to **1b**. After standing several days at ambient temperature, HPLC and NMR[18] indicated a 4:1 mixture of **1b** and **2b**.

Acknowledgment. Dr. D. B. Boyd provided assistance with SYBYL and comments on the manuscript, Mr. J. Niemeier and Mr. D. Creeden performed the calorimetry, and Dr. W. D. Luke reviewed the manuscript and participated in lively discussions.

Supplementary Material Available: Atomic coordinates, equivalent isotropic displacement parameters, bond lengths, bond angles, and anisotropic displacement parameters for compound **3b** (5 pages). Ordering information is given on any current masthead page.

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Reactions of Lithiooxazole

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Received April 20, 1990

Recent research in our laboratory has been directed toward the preparation of symmetrical bis(oxazolyl)-methanols, 1–3, as fragments of larger synthetic targets. A simple strategy for their synthesis would involve regioselective generation of isomeric lithiooxazoles and

0022-3263/91/1956-0449$02.50/0