Structure of Penem Sulphoxide

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Oxidation of the penem derivative (**1a,b**) by *m*-chloroperbenzoic acid occurs by the direction of the β-lactam carbonyl oxygen to give β-sulphoxide (**2a,b**) as a major product, whose structure has been determined by *X*-ray crystallography.

Oxidation of penicillins and cephalosporins with peracid to their sulphoxides has been well studied; substituents α to the β-lactam carbonyl have a great influence on its stereoselectivity. The amide proton of the 6β-acylamide group generally directs the attack of peracid from the β-side (concave face), whereas bulky groups which have no amide proton, such as phthalimide, have a steric effect, affording α-sulphoxide from the less hindered side attack.[1] It has also been observed that 6α-bromopenicillanic acid is converted to the β-sulphoxide whereas its 6β-isomer is oxidised to α-sulphoxide.[2] Recently, Bycroft *et al.* reported the selective formation of the β-sulphoxide of a 6-spiropenam derivative by peracid oxidation.[3]

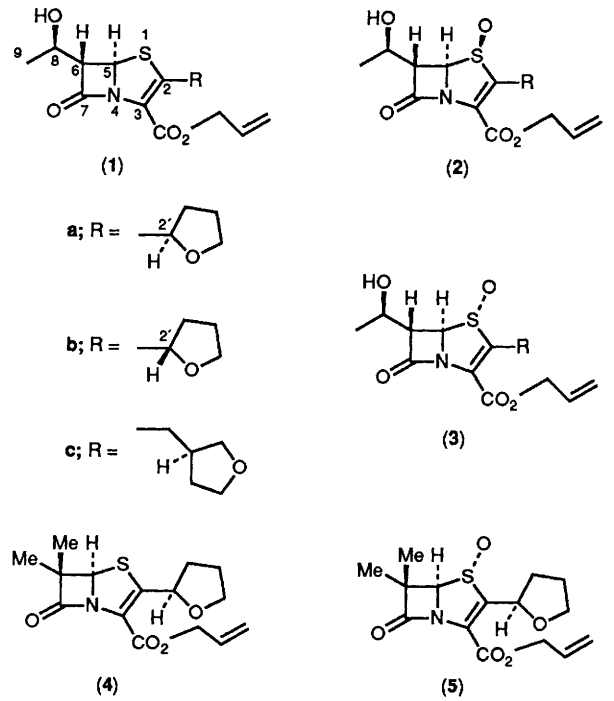
Penem, a new congener of β-lactam antibiotics, and its derivatives can also be oxidised to the sulphoxide,[4] although the exact configuration has not yet been elucidated.

In the course of our studies of penem antibiotics, we have observed high stereoselectivity in the peracid oxidation of the sulphur atom in the penem nucleus to its sulphoxide. We herein report on the elucidation of the configuration of the penem sulphoxide and describe the stereochemical origin of this reaction.

The penem derivative (**1a**)[5] was treated with *m*-chloroperbenzoic acid (*m*-CPBA; 1 equiv.) in CH_2Cl_2 to give a mixture of penem sulphoxides (**2a**) and (**3a**) (ratio 4 : 1), which were easily separated by silica gel chromatography. The oxidation of the 2′-epimer (**1b**) under the same conditions provided a mixture of the penem sulphoxides (**2b**) and (**3b**) in a similar ratio. This selectivity was not affected by the protection of the hydroxy at C-8 by the t-butyldimethylsilyl moiety. The IR (1784, 1725, and 1055 cm^{-1}), UV ($\lambda_{max.}$ 298 nm), and FAB mass spectra [*m/z* 342, (M^+ +1)] of the major product (**2a**) supported the sulphoxide structure and ^1H NMR spectroscopy indicated the diastereoisomeric sulphoxide structure for the minor product.†

The major diastereoisomer (**2a**) shows a higher field shift (δ 4.84) for the C-5 proton compared to that of the minor isomer (**3a**) (δ 4.96), while the C-6 proton appears at lower field (δ 3.86) in (**2a**) compared to (**3a**) (δ 3.73), so do the protons of (**2b**) and (**3b**), suggesting the attack of *m*-CPBA on the same side. However, these data did not give the exact assignment of the configuration of each sulphoxide. A suitable crystal of the major sulphoxide (**2a**) for *X*-ray crystallographic analysis was obtained by recrystallisation from tetrahydrofuran.‡ Recrystallisation of the other major sulphoxide (**2b**) also gave a good crystal for *X*-ray structural analysis.

X-Ray crystallography unambiguously gave the β-sulphoxide structure for the major product (**2a**) (Figure 1) and for the sulphoxide (**2b**). This indicates the preference of β-side



† All new compounds exhibited satisfactory ^1H and ^{13}C NMR, IR, and mass spectra.

‡ *Crystal data* for (**2a**): $C_{15}H_{19}O_6NS$, M = 341.38, monoclinic, space group $P2_1$, a = 9.762(1), b = 13.794(1), c = 6.133(1) Å, β = 94.11(1)°, U = 823.7 Å^3, Z = 2, D_c = 1.377 g cm^{-3}, 1395 independent reflections (sin θ/λ <0.58 Å^{-1}) were collected on Rigaku automatic four-circle diffractometer using Cu-K_α radiation. The R factor is 0.042 for 1394 observed reflections. The structure was solved by direct methods (MULTAN 84) and block-diagonal least-square refinement methods. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

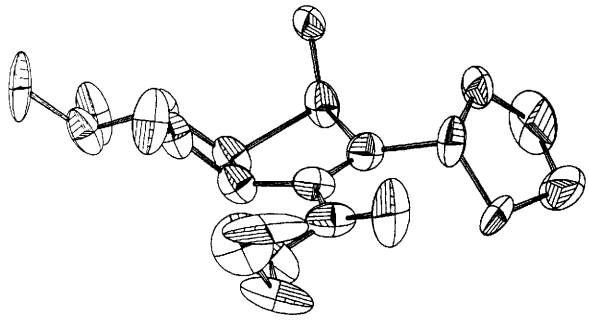


Figure 1. Perspective view of the crystal structure of (**2a**).

(concave face) attack of the reagent (*m*-CPBA) at the sulphur atom in the penem nucleus. The configuration of the penem sulphoxides could be conveniently determined by comparison of the chemical shifts of *trans* protons at C-5 and C-6 in their ^{1}H NMR spectra. Thus, the major sulphoxide of penem (**2c**) can be assigned to have β-configuration at S-1, from comparison of the ^{1}H NMR spectrum with that of its isomer. This unexpected selectivity indicated the importance of directional effects other than steric effects, since the β-side is a concave face which should be sterically more hindered than a convex face.

An isoelectronic potential field calculation using a proton probe[6] showed the most favourable site for a hydrogen bond at the β-lactam carbonyl oxygen (−29.4 kcal mol^{-1}; 1 kcal = 4.184 kJ) and weak favourable sites at the tetrahydrofuran oxygen (−21.3 kcal mol^{-1}) and hydroxy oxygen (−20.3 kcal mol^{-1}), indicating that the β-lactam carbonyl oxygen assisted the β-face attack of peracid (*m*-CPBA) on the sulphur atom of penem.

It was found that the preference of *m*-CPBA for β-face attack on penem (**1a**) is reduced to a 3 : 2 ratio of β to α when the solvent is changed from dichloromethane to ethyl acetate. This strongly confirms the role of the β-lactam carbonyl group in directing the β-face attack of the reagent by its electrostatic character. This β-face directional effect of the β-lactam carbonyl oxygen originates from its location on the β-side of the thiazoline ring and the puckered conformation of β-lactam ring, the carbonyl oxygen of which is 0.27 Å out of the plane formed by N-4, C-5, and C-6 towards its β-side (see Figure 1). This directional effect would be also disturbed by introduction of substituents at the 6β-position. Thus, the oxidation of the 6,6-dimethylpenem derivative (**4**) gave, exclusively, the rather unstable α-sulphoxide (**5**) whose structure was deduced from its UV spectrum, which showed a characteristic absorption at 333 nm.

These results give evidence for the participation effects of the β-lactam carbonyl oxygen in addition to steric and hydrogen bonding effects of 6β-substituents such as halogen, alkyl, and acylamide groups as reported previously.[1—3] This effect of the carbonyl oxygen in a puckered β-lactam conformation will be a common phenomenom in β-lactam chemistry such as β-face selectivity in the aldol-type reaction at the C-6 position of penam derivatives.[7] Details of studies of this aldol selectivity will be reported elsewhere.

Deprotection of the allyl group[8] of the sulphoxides (**2a**) and (**2b**), using $(PPh_3)_4Pd$ and dimedone[9] in ethyl acetate, afforded the corresponding sodium salts. These sodium salts were too unstable at physiological pH to measure their microbiological activity, but were rather stable at lower pH (5.5), showing weak activity against Gram positive and negative bacteria.

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