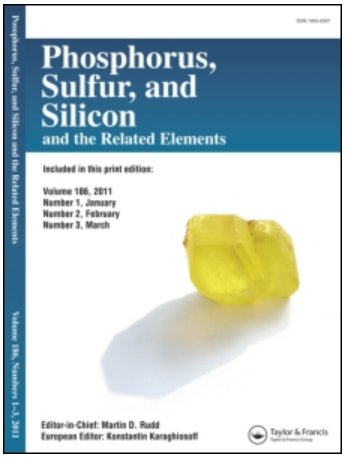

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Kupka, T. , Małecki, J. G. , Lodowski, P. , Jaworska, M. and Dzięgielewski, J. O.(1994) 'Sulfur Ligands. from β-Lactam Antibiotics to Contrast Agents for MRI', Phosphorus, Sulfur, and Silicon and the Related Elements, 95: 1, 505 — 506
To link to this Article: DOI: 10.1080/10426509408034295
URL: http://dx.doi.org/10.1080/10426509408034295

Phosphorus, Sulfur, and Silicon, 1994, Vol. 95–96, pp. 505–506
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SULFUR LIGANDS. FROM β-LACTAM ANTIBIOTICS TO CONTRAST AGENTS FOR MRI

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Abstract NMR, IR and semi empirical Molecular Orbital PM3 studies on selected β-lactam antibiotics are reported. The role of sulfur in β-lactam antibiotics is discussed.

INTRODUCTION

β-lactam antibiotics[1-2] (penicillins and cephalosporins) are sulfur containing drugs. The mechanism of their antibacterial action in vivo and transition metal ion promoted hydrolysis in vitro are similar. The presence of four membered β-lactam ring in their molecular structure is responsible for their biological action and in vitro reactivity (instability). According to Woodward suggestion[1], the inhibited amide resonance of β-lactam bond, caused by the presence of 5- and 6- membered rings, for penicillins and cephalosporins, respectively results in weakening of this bond. Hence, the corresponding C7 - N4 bond in β-lactams is longer than in typical amides (planar geometry at the nitrogen atom). Moreover, the increase of positive charge at atom C-7 indicates higher susceptibility of the drug to nucleophilic attack, and, in consequence, higher activity in vivo. NMR and IR are sensitive methods, able to monitor the presence of intact β-lactam moiety. NMR is also suitable to study the metal - ligand interaction in solution. Theoretical calculations on β-lactams, both at semi empirical (older methods without parametrisation for sulfur atom and for very simplified models) and ab initio level (with low basis sets) have been reported.
This work discusses our systematic NMR, IR and semi empirical PM3 studies on model penicillins. The role of solvent, self-association and micellation is emphasised and the possible metal ion binding sites are discussed.

RESULTS AND DISCUSSION.

The presence of hydrogen bonding and formation of micellar solutions of cloxacillin in heavy water was concluded from ^{1}H and ^{13}C NMR data[3]. Both NMR and IR data[3-4] indicated formation of $COO\text{-}M^{+}$ and $COO\text{-}M^{+}\text{-}N_4$ complexes in solution (M^{+} is di- or trivalent transition metal ion). There was no indications on M-L interations at the sulfur atom. PM3 calculations on methylpenicillin (ref. 5 and works cited therein) indicated the weakening of β-lactam bond upon protonation of the compound. The mentioned bond

is shorter in Pen-COO^- than in PEN-COOH, or, with the presence of bound zinc ion. This was accompanied by the increase of positive Mulliken charge at C_7. The replacement of sulfur by O, NH and CH_2 was also studied at the PM3 level. This method is believed to be superior both in predicting the correct geometry and energy of larger molecules of biological interest. The corresponding changes of β-lactam bond lenght are shown in Figure 1. The calculated differences are very small, however, there are some trends which are in agreement with classical understanding of β-lactam reactivity. The predicted heats of formation, C_7-N_4 and C_7-O_8 bond lenghts and Mulliken charges at C_7 are more sensitive to changes in the ionizing state of the molecule (Pen-COOH vs. Pen-COO^-).

On the other hand, D-penicillamine interacts with transition metal ions both via S and NH_2 donor groups. This amino acid is formed during penicillin degradation. It has been used in medical treatment to remove heavy metal ions from human body. Formation of stable, water soluble complexes with some metal ions is promising for the modern medical diagnostic methods. Hence, we can expect[6] its use in design of new contrast agents for magnetic resonance image (RMI).

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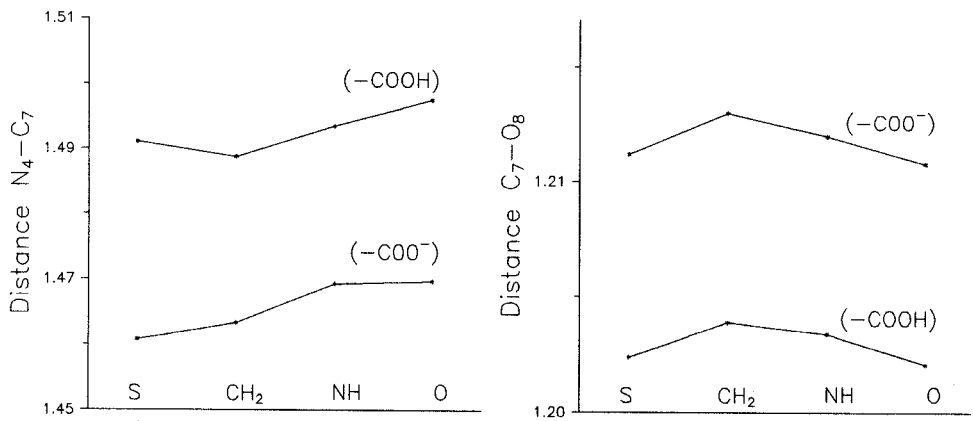

FIGURE 1. Changes in C_7-N_4 and C_7-O_8 bond lenghts upon sulfur replacement.