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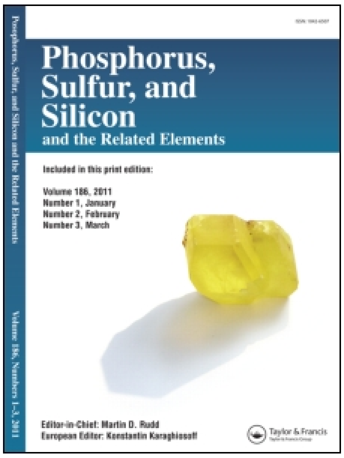

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A ^{31}P NMR Study of the Stability of Carboxyifosfamide and Carboxycyclophosphamide, Two Metabolites of Ifosfamide and Cyclophosphamide

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A ^{31}P NMR STUDY OF THE STABILITY OF CARBOXYIFOSFAMIDE AND CARBOXYCYCLOPHOSPHAMIDE, TWO METABOLITES OF IFOSFAMIDE AND CYCLOPHOSPHAMIDE

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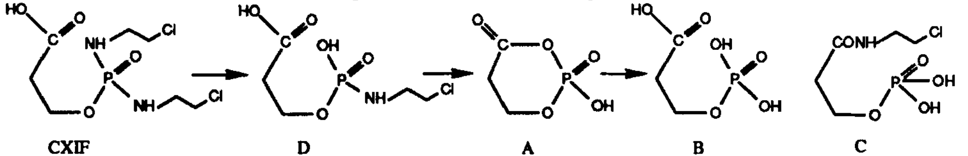
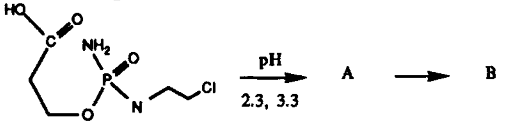
Ifosfamide (IF) and cyclophosphamide (CP) are two phosphorated anticancer agents used in the treatment of solid tumours. Several phosphorated metabolites, among them carboxyifosfamide (CXIF) and carboxycyclophosphamide (CXCP), were detected and quantified by ^{31}P NMR in urine from patients treated with IF or CP. In agreement with other authors [1], we observed a great inter-patient variability in the urinary excretion of CXIF in patients treated with IF [2]. This variability was attributed to a genetic polymorphism of aldehyde dehydrogenase, the enzyme responsible for the formation of CXCP or CXIF [1,3]. Since CXCP and CXIF are unstable, we thought that the inter-individual variability could also be due to a degradation during the storage of urine samples. A ^{31}P NMR study of the stability of CXIF and CXCP in urine as a function of time, pH (7 and 5.5) and storage temperature (25°C, 8°C, -20°C, -80°C) demonstrated that (i) CXCP and CXIF are more stable at pH 7 than at pH 5.5, (ii) CXCP is more stable than CXIF at both pH, (iii) the degradation decreases with temperature but still occurs at -20°C and even -80°C. For an accurate quantification of these compounds, the storage of urine samples must be done at -80°C immediately after collection and not exceed 1 month at pH 7 whereas, at pH 5.5, the assay must be carried out in the few days following the sampling. To identify the degradation products of CXCP and CXIF, the time course of hydrolysis (between pH 2 and 7) of these compounds was monitored by ^{31}P NMR. The structure of each compound formed was determined by mass spectrometry and ^{1}H and ^{13}C NMR after their isolation (except compound A too unstable to be isolated). The results are reported in the following schemes.



CXIF D A B C

B was detected at all pH (2.3, 3.3, 4.2, 5.6, 7.0), D only at pH 4.2, 5.6 and 7.0, A at pH 2.3, 3.3, 4.2, 5.6 and C at pH 3.3, 4.2, 5.6.



CXCP

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