ENVIRONMENTALLY RELEVANT TRANSFORMATIONS OF PHARMACEUTICALS MONITORED BY NMR SPECTROSCOPY

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Reaction mechanism details of chlorination and hydrolysis of anticancer agents cyclophosphamide (**CPA**) and ifosfamide (**IF**) have been zoomed in by the use of 1D- (^{1}H, ^{13}C, and ^{31}P) and 2D-NMR techniques. During acid catalyzed hydrolysis of **IF**, the stable intermediate was observed and its structure was resolved by HMBC and HSQC spectra (see Figure). In contrast, no intermediate was detected in the course of the hydrolysis of **CPA**, suggesting different reaction mechanisms for the two pharmaceutical isomers.

Both **CPA** and **IF**, in the absence of light (in the darkness of the magnet), undergo *N*-chlorination reaction, resulting in *N*3- and *N*7-chlorinated products, respectively. However, when exposed to UV light, the reaction rate is decreased and the chlorination inhibited. This may be due to light sensitivity of the product.

To perform chlorination in the presence of UV-light (380 nm) and/or white light (400-750 nm), the optical fiber, connected to the respective light source, was inserted in NMR tube containing reaction mixture (**CPA**/**IF** and HOCl). A coaxial NMR tubes system was used in which the fiber was not immersed directly in solution. To monitor reactions with increased rate, a two-chamber borosilicate glass NMR tube, which allows for in-tube mixing, was used.

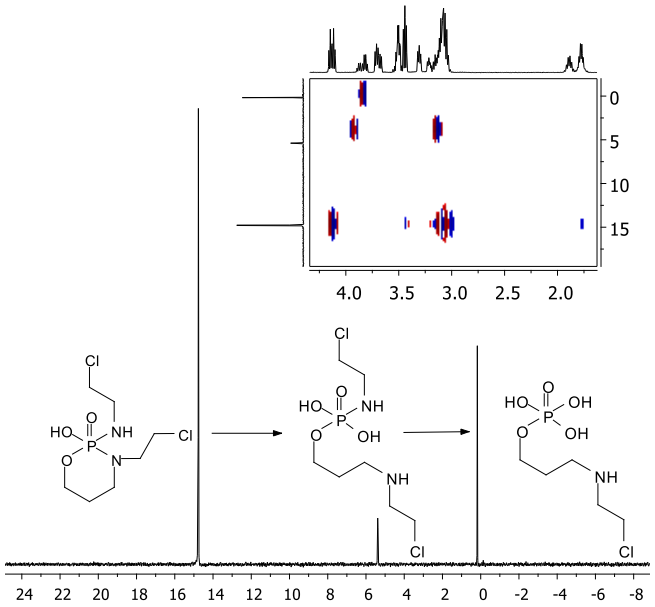

Figure. ^{31}P{^{1}H} and gHMBC (^{1}H-^{31}P) NMR spectra of the reaction mixture (ifosfamide/HOCl/D_2O)

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