QSAR STUDY OF THE FATE OF PHARMACEUTICAL CHEMICALS IN AN AQUATIC ENVIRONMENT

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Many pharmaceutical chemicals, both active drugs and adjuvants, are disposed of through the main sewage system and may thus contaminate drinking water unless they are degraded in the sewage treatment works or elsewhere (Richardson and Bowron 1985). Most biodegradation occurs *via* bacterial enzymes, and thus should be amenable to QSAR analysis in much the same way as any other biological activity (Kaiser 1984).

One measure of biodegradation is biological oxygen demand (BOD), and we have attempted to correlate this with a number of appropriate physicochemical and structural properties, for several series of compounds of pharmaceutical importance. Among the parameters investigated was atomic charge, calculated using the CINMIN program following energy minimisation *via* molecular mechanics. The charge difference, ignoring sign, ($\Delta|\delta_{AB}|$) across selected bonds was found to correlate extremely well with 5-day BOD values (expressed as % of theoretical maximum BOD). Other more commonly used parameters such as log P, steric terms and molecular connectivity generally contributed little or nothing to the correlations obtained. We give below some examples of the correlations that have been achieved with series of compounds of pharmaceutical importance, using the charge difference across the C-O bond in each case. Charge differences across other bonds gave very poor correlations.

Aliphatic alcohols (with straight and branched chain alkyl, benzyl and chloro substitution)

$$BOD = 0.575\ (\Delta|\delta_{CO}|x10^4) - 2.189$$

$$n = 19 \quad r = 0.989 \quad s = 3.790 \quad F_{1,17} = 767.6$$

Glycols (with straight chain alkyl substitution)

$$BOD = 1.004\ (\Delta|\delta_{CO}|x\ 10^4) + 0.510$$

$$n = 5 \quad r = 0.997 \quad s = 2.281 \quad F_{1,3} = 437.2$$

n = no. of compounds; r = correlation coefficient; s = standard error; F = variance ratio

The extremely good correlations of biodegradability with charge difference across the C-O bond clearly indicate that, in these series of compounds, electronic factors control the biodegradation, and that lipophilicity and (perhaps surprisingly) steric factors play a negligible part. The work should enable the biodegradability of other compounds within the same classes to be readily predicted.

Kaiser, K.L.E. (1984) Environment International 10: 241-250
Richardson, M.L., Bowron, J.M. (1985) J. Pharm. Pharmacol. 37: 1-12

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