The Effect of Halogenation on Membrane Partitioning and Permeation

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Halogenation of drugs is commonly used to enhance membrane binding and permeation. We quantify the effect of replacing a hydrogen residue, -H, by a chlorine, -Cl, or a trifluoromethyl residue, $-CF_3$ in position C-2 of promazine, perazine, and perphenazine analogs. Moreover, we investigate the influence of the position (C-6 and C-7) of residue $-CF_3$ in benzopyranols. The twelve drugs are characterized by surface activity measurements which yield the cross-sectional area, A_D, the air-water partition coefficient, K_{aw}, and the critical micelle concentration, CMC_D [1]. Using the first two parameters (A_D and K_{aw}) and the appropriate membrane packing density, π_M, the lipid-water partition coefficients, K_{lw}, are calculated [2] in excellent agreement with the lipid-water partition coefficients measured by means of isothermal titration calorimetry for small unilamellar vesicles of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine []. Replacement of a hydrogen residue by a chlorine and a trifluoromethyl residue enhances the free energy of partitioning into the lipid membrane, on average by $\Delta G_{lw} \approx -1.3$ kJ/mol and $\Delta G_{lw} \approx -4.5$ kJ/mol, respectively. The permeability coefficient, P, estimated on the basis of Stokesian diffusion [4], increases by a factor of ~2 and ~9, respectively. Despite exhibiting practically identical hydrophobicities, the two benzopyranol analogs differ in their permeability coefficients by almost an order of magnitude, which is due to their different cross-sectional areas, A_D, at the air-water and lipid-water interface.

References

[1] Seelig A, Gottschlich R, Devant RM. Proc. Natl. Acad. Sci. USA 91: 68-72, 1994

[2] Fischer H, Gottschlich R, Seelig A, J. Membrane Biology 165: 201-211, 1998

[3] Gerebtzoff G, Li Blatter X, Frentzel A, Seelig A. ChemBioChem 5: 676-684, 2004

[4] Seelig A, Gatlik-Landwojtovicz E. Hot Topics Issue/Mini-Reviews in Medic. Chem., in press