THE SOLUBILITY OF BENZODIAZEPINES IN SODIUM SALICYLATE SOLUTION AND A PROPOSED MECHANISM FOR HYDROTROPIC SOLUBILIZATION

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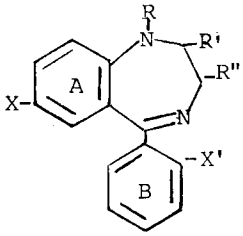
Hydrotropic salts had been used to increase the solubility of a number of drugs (Ueda 1966). As information on the influence of various substituents on the solubilization of structurally related compounds by hydrotropic salts is still lacking, we report here the effect of simple structure modification on the solubility of a series of poorly soluble benzodiazepine derivatives in sodium salicylate solution (Table 1).

Table 1. Structure of benzodiazepine derivatives under study and their solubilities in 1.87M sodium salicylate solution.



Name	X	X'	R	R'	R"	$Mx10^3$
Diazepam	Cl	H	CH_3	O	H	27.6
Medazepam	Cl	H	CH_3	H	H	11.9
Oxazepam	Cl	H	H	O	OH	7.9
Nitrazepam	NO_2	H	H	O	H	18.4
Clonazepam	NO_2	Cl	H	O	H	5.1

Results indicate that substituents affecting the electron density on the 7-membered ring of the benzodiazepine molecule have a considerable effect on solubility. Decrease of the electron density due to the carbonyl oxygen at C_2 could account for the higher solubility of diazepam compared to medazepam. However, the relatively low solubility of oxazepam may be attributed to the involvement of the carbonyl oxygen at C_2 and the additional hydroxyl group at C_3 in intermolecular hydrogen bonding. The influence of a chlorosubstituent at C_2 can be seen when comparing the solubility of clonazepam and nitrazepam, the former being less soluble. A nitrosubstituent at C_7 resulted in the lower solubility of nitrazepam compared to diazepam having a chlorosubstituent in the same position. These results and visible spectral studies of medazepam indicate that an electrostatic force of the donor-acceptor type (Higuchi & Drubulis 1961) between sodium salicylate and the benzodiazepine molecules plays an important role in the solubility of these compounds. The effect of substituents can be explained on the basis of donor-acceptor type interactions.

McKee (1946) suggested that hydrotropy is a salting-in effect, while Ueda (1966) indicated the formation of a complex at lower concentrations. The above explanations fall short of giving an overall mechanism for hydrotropy. Consequently a mechanism for solubilization by hydrotropes is here proposed involving aggregation of the hydrotrope.

The conductance of sodium salicylate, sodium benzoate, and potassium phthalate plotted versus concentration exhibits a discontinuity strongly indicative of association. Sodium salicylate was found to have the highest aggregation concentration followed by sodium benzoate and potassium phthalate in the range 0.028 to 0.670M. The effect of temperature on sodium salicylate aggregation was also studied and the plot of aggregation concentration against temperature was similar to that of ionic surfactants. Aggregation concentrations obtained from conductivity measurements were in good agreement with the results of viscosity and diffusion methods.

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