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ABILITY OF THE ACETOTOLUIDES TO FORM CYCLODEXTRIN INCLUSION COMPLEXES.

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INTRODUCTION.

Cyclodextrins (CDs) are capable of conferring advantageous properties on guest molecules that are able to penetrate and reside within the CD cavity. Hence the increasing importance of CDs in the pharmaceutical industry.

When assessing the potential of a guest molecule to form a CD inclusion complex, the ability of that guest molecule, or a portion of the molecule, to penetrate the CD cavity is crucial. To help elucidate the type of chemical structure best able to form inclusion complexes with CDs, the behaviour of the acetotoluides (o-, m- and p-ACT, see Figure 1) with α- and β-CD has been investigated in aqueous solution and in the solid state.

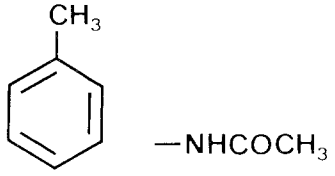

Figure 1 Structure of the Acetotoluides (ACTs)

METHODS.

Solubility Studies allow molecular interactions to be studied by means of solubility measurements. Increasing amounts of CD are added to a constant amount (in excess of its normal solubility) of ACT in pH 5 acetate buffer. After equilibration, the solvent may be analysed for ACT and the equilibrium constant of the reaction may be calculated from the slope of the graph of concentration of ACT against concentration of CD (presuming complex stoichiometry is

1:1, from Higuchi and Connors, 1965).

Filtration Cell Studies rely on a molecular weight-specific membrane retaining complexed molecules but allowing free passage of uncomplexed molecules. α-CD has a molecular weight of 972, β-CD of 1135. An ultrafiltration membrane with a molecular weight cut-off value of 1000 will therefore retain a large percentage, if not all, of the CD. The molecular weight of the ACTs is 149. The passage of ACT through such a membrane should therefore be unhindered. If, however, ACT forms a complex with CD, then it should be retained by the membrane. This is the basis of the method of detection of inclusion complexation by the filtration cell (see Jones and Parr 1983 and 1985).

Thermal Analysis (by differential scanning calorimetry) utilises the fact that if a crystalline inclusion complex is formed between CD and ACT, it will have different crystalline properties to the components of the complex. The difference in melting point between the complex components and the complex itself may therefore be detected.

RESULTS.

Solubility Studies. All the ACT isomers exhibited an increase in solubility with increasing concentrations of both α- and β-CD. Table 1 (below) contains the slope of each line (concentration of ACT against concentration of CD), as calculated by linear regression, and the equilibrium (stability) constant for each interaction.

	α-CYCLODEXTRIN		β-CYCLODEXTRIN	
ACT ISOMER	SLOPE	EQUILIBRIUM CONSTANT	SLOPE	EQUILIBRIUM CONSTANT
ORTHO	0.518	17.1	0.453	13.0
META	0.278	10.0	0.639	43.3
PARA	0.153	31.3	0.402	99.0

Table 1 Interaction of the ACT isomers with α- and β-CD in pH 5 buffer at 30°C

The interaction of o- and m-ACT with α-CD is just detectable, and although the equilibrium constant between p-ACT and α-CD is greater, the interaction is again weak. The ACT structure is therefore not compatible with the internal cavity of α-CD. However, interaction of β-CD with the ACTs is stronger and follows a more logical pattern : o- < m- < p-ACT. This seems to indicate that the benzene ring of the guest molecule will enter the cavity of the β-CD host molecule methyl group first. The acetamido group is too large to allow penetration of the entire ACT molecule into the CD cavity. If the

acetamido group is in the para position however, this allows the benzene ring of some ACT guest molecules to reside within the β-CD cavity.

Filtration Cell Studies. By assaying the filtrate of the filtration cell, the percentage (by weight) of ACT isomer appearing in the filtrate when filtered alone and in the presence of α- and β-CD could be calculated. These results supported those of the solubility studies, i.e. there was little or no interaction of the ACTs with α-CD and a graded response of o- < m- < p-ACT with β-CD.

Thermal Analysis of the inclusion complex components, their physical mixtures and the freeze dried powders (used to prepare the inclusion complexes) confirmed that whilst all ACTs formed complexes with β-CD, none did with α-CD. It was difficult to conclude from the thermograms which, if any, ACT isomers were more compatible with the β-CD cavity than others.

CONCLUSION

These series of experiments have shown that the α-CD cavity was too small to allow stable inclusion complex formation. p-ACT is the isomer within this series that is best able to form inclusion complexes with β-CD, then m-ACT and finally o-ACT. This would seem to indicate that the benzene ring of the molecule is the part of the structure most likely to penetrate the cavity since (a) α-CD could not form stable complexes with any of the guest molecules and (b) less effective entry into the β-CD cavity is the result of the acetamido group moving from p- → m- → o- positions. Benzene ring penetration of the CD cavity is therefore required for stable inclusion complex formations in this group of compounds.

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