

INVESTIGATION OF SOLUTE-SOLVENT COMPLEXES INVOLVING TESTOSTERONE AND TESTOSTERONE PROPIONATE, USING SOLUBILITY RESULTS

K.C. James and M. Mehdizadeh, Welsh School of Pharmacy, UWIST Cathays Park, Cardiff, CFL 3NU.

Complexation has been detected between various organic solvents and androgens and androgen esters, by i.r. spectrophotometry (James et al, 1971, 1975). Whilst the technique can identify the types of complexes which are formed, it is not easily adaptable to the evaluation of association constants and thermodynamic parameters of complexation. In addition, the method fails when the solvent absorbs in the critical region of the spectrum. It is particularly unfortunate that this problem occurs with ethyl oleate and octanol, because these have been used in biological studies which could be correlated with complexation data.

Complexation can be studied by following the effect of the complexing agent on the solubility of the substrate (Higuchi & Connors, 1965). Solubilities $(A)_t$ are determined in an inert solvent in the presence of increasing quantities of complexing agent $(B)_t$. If 1:1 complexation occurs, $(A)_t$ should be related rectilinearly to $(B)_t$, and the association constant can be calculated from the slope.

This treatment is applicable to solid complexing agents, because their effect on the solubility of the unassociated substrate is negligible. However, liquid complexing agents are solvents in their own right, and also increase the volume of the equilibrium mixture. The solubility in the pure inert solvent, cannot therefore be assumed to be independent of complexing agent concentration, unless it is so small that changes are negligible in comparison with $(A)_t$. The solubility of testosterone in pure *c*-hexane was considered sufficiently small, and plots of $(A)_t$ against $(B)_t$ in *c*-hexane/octanol and *c*-hexane/ethyl oleate blend were, in fact, rectilinear over almost the whole concentration range. Association constants were calculated from these.

The corresponding plot for testosterone propionate in *c*-hexane/octanol mixtures was parabolic. Similar behaviour has been reported for other systems, and attributed to the complex reaching a limiting solubility. It is more probable that this plot represents simple regular solution behaviour, since calculated regular solubilities (X_2) yielded a similar plot to $(A)_t$, and in all cases X_2 exceeded $(A)_t$. When solute-solvent complexation occurs observed solubilities should be higher than regular solubilities. Further evidence against complexation with octanol comes from the behaviour of testosterone propionate in carbon disulphide and carbon tetrachloride. It is known from i.r. evidence that these solvents do not complex with testosterone propionate. Rectilinear plots of $(A)_t$ against $(B)_t$ were obtained, but yielded apparent association constants of only about 0.5. Both plots ran parallel to and below those obtained with calculated regular solubilities. Final support for the regular solution approach comes from the fact that ethyl oleate gave a similar pair of plots to octanol. It is difficult to contemplate any form of charge-transfer process between this solvent and testosterone propionate.

Application of the solubility technique to systems which are known to form complexes higher than 1:1 (e.g. testosterone propionate in chloroform), gave results which were in line with the i.r. evidence, and which could be used to calculate 1:2 association constants.

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