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An infrared study of solute-solvent interactions of testosterone propionate

K. C. JAMES AND P. R. NOYCE

Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cathays Park, Cardiff, U.K.

Interactions between testosterone propionate and 10 different organic solvents have been investigated by observing the shifts of the stretching frequencies of the ketone and ester carbonyl groups. The shifts are shown to be approximately proportional to the degree of deviation from regular solution behaviour. The solvents are classified into three groups and the possible interactions in each discussed.

In a study of the solubilities of testosterone propionate in various solvents (Bowen & James, 1970), a plot of the ratios of experimental to calculated solubilities against temperature indicated that the solvents fell into two different groups. The difference between these groups was accounted for in terms of entropy, from which a postulate was made that specific solute-solvent interactions occurred in one of the groups. We have used infrared spectroscopy to investigate these interactions since the shifts in frequency of a particular group vibration are indicative of the energy changes occurring when that group interacts with another (Badger & Bauer, 1937; Searles, Tamres & Barrow, 1953). In testosterone propionate the reactive groups are the Δ^4-3-ketone and the ester carbonyl on the 17β-side chain; the stretching bands ($\nu_{C:O}$) of these dipoles have been examined by scanning in the 1770–1650 cm^{-1} region.

EXPERIMENTAL

Testosterone propionate was a gift from Organon Laboratories Ltd. *cis*- and *trans*-1,2-Dichloroethylenes were Eastman Kodak solvents, other substances were obtained from British Drug Houses Ltd. Solvents were dried over either sodium or anhydrous calcium chloride and those below 99·0% purity were fractionally distilled. Spectra were run on a Perkin-Elmer 521 grating spectrophotometer, using a linear scale expanded by a factor of 10. On over 80 preliminary measurements made to test reproducibility not one determination varied from the mean by more than $\pm 0{\cdot}5$ cm^{-1}. Sodium chloride cells (0·1 mm) were used with cyclohexane placed in the reference beam.

Binary solvent systems were selected to give a complete concentration range of each component solvent from pure cyclohexane to the pure solvent under investigation. Each sample was 0·12M with respect to testosterone propionate and was prepared by weighing into a 5 ml ampoule, which was sealed immediately to prevent evaporation of volatile components.

RESULTS AND DISCUSSION

The shift in frequency of a particular vibration upon a change of environment has led to various theories, for example, Kirkwood (see West & Edwards, 1937), Bauer & Magat (1938) and Buckingham (1958). As a measure of the shift these workers

used the difference between the frequency of the vibration in the vapour state and that in a solution of the solvent being examined. It has been suggested by Horak & Plíva (1965) that to compare the frequency of a particular group in a non-polar solvent with that in a polar one is of doubtful validity, since the interactions involved are different. Having studied the solvent effect of some saturated hydrocarbons on the respective carbonyl stretching bands of testosterone propionate under high resolution and found no observable shift, we decided to adopt cyclohexane as an arbitrary standard; the shift $\Delta\nu_{C:O}$ then represents the parameter ($\nu_{cyclohexane} - \nu_{solvent}$). The frequencies of both the conjugated ketone and the ester groups in various solvents, together with the respective shifts are in Tables 1 and 2.

Table 1. *Effect of solvents on* Δ^4*-3-ketone group stretching frequency*

Solvent	Frequency of peak in pure solvent (cm^{-1})	Shift (cm^{-1})	Number of complexes	Isosbestic points (cm^{-1})
Chloroform	1662·1	21·8	2	1682·0 1676·5
trans-1,2-Dichloroethylene	1667·0	16·9	1	1682·5
cis-1,2-Dichloroethylene	1668·0	15·9	1	1681·7
1,2-Dichloroethane	1668·5	15·4	2	1681·9 1676·6
Nitrobenzene	1673·5	10·4	1	1681·8
Chlorobenzene	1677·0	6·9	1	1681·8
Benzene	1678·6	5·3	1	1682·2
Toluene	1679·4	4·5	1	1682·0
Carbon disulphide	1678·9	5·0	—	—
Carbon tetrachloride	1679·8	4·1	—	—

Table 2. *Effect of solvents on* 17β*-ester group stretching frequency*

Solvent	Frequency of peak in pure solvent (cm^{-1})	Shift (cm^{-1})	Number of complexes	Isosbestic points (cm^{-1})
Chloroform	1727·8	17·8	1	1739·8
cis-1,2-Dichloroethylene	1729·8	15·8	1	1741·4
1,2-Dichloroethane	1730·2	15·4	1	1741·4
trans-1,2-Dichloroethylene	1732·2	13·4	1	1741·4
Nitrobenzene	1731·7	13·9	1	1742·4
Chlorobenzene	1733·5	12·1	1	1742·0
Benzene	1737·6	8·0	1	1742·0
Toluene	1738·7	6·9	1	1742·7
Carbon disulphide	1738·7	6·9	—	—
Carbon tetrachloride	1738·8	6·8	—	—

Earlier work on ketones (Whetsel & Kagarise, 1962) had demonstrated that proton-donating solvents, such as chloroform, may form hydrogen bonds with a carbonyl group. We investigated chloroform, using a similar technique of ternary systems in which the polar solvent progressively replaces cyclohexane (James & Noyce, 1970). We have now extended the study to other solvents. The position of the isosbestic points and the number of specific complexes proposed are in Tables 1 and 2.

The solubility of a substance depends largely on the type and magnitude of its interactions with the solvent. These interactions affect the bond strength within the dipolar moiety involved, which is expressed as a decrease in the force constant

characterized by a spectral shift of the group vibration under consideration. We have inferred from our results that the intermolecular forces acting on both the ester group and the Δ^4-3-ketone are similar in type and magnitude. Since the relative contributions of the groups to the total interacting potential of the steroid molecule could not be ascertained, the shifts of the two groups were added together and plotted against the ratio of the experimental to the calculated solubility for each solvent in an attempt to correlate spectral data with solubility (Fig. 1). The graph suggests a correlation and shows that three distinct groups of solvents are discernible: partially chlorinated hydrocarbons, aromatics and completely substituted derivatives of methane.

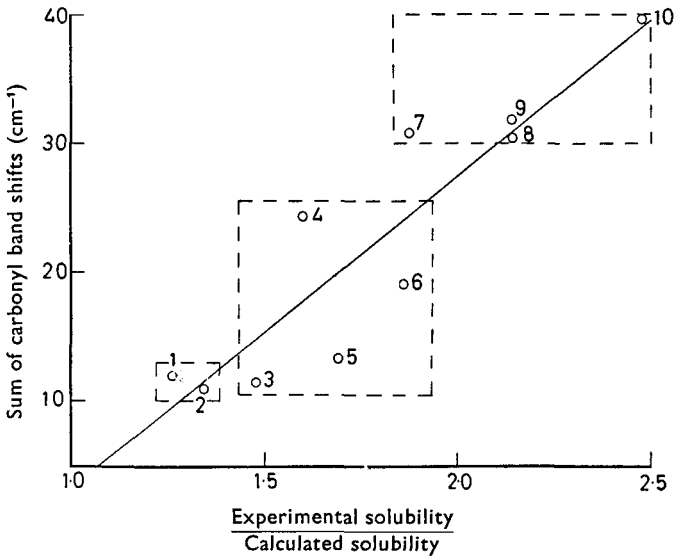

FIG. 1. Correlation between solubility and spectral shift. 1. Carbon disulphide. 2. Carbon tetrachloride. 3. Toluene. 4. Nitrobenzene. 5. Benzene. 6. Chlorobenzene. 7. 1,2-Dichloroethane. 8. *trans*-1,2-Dichloroethylene. 9. *cis*-1,2-Dichloroethylene. 10. Chloroform. All shifts are the mean of three results. Solubility data are from Bowen (1969).

The chlorinated hydrocarbons as a group are responsible for the largest spectral shifts. The formation of hydrogen bonds between chloroform and testosterone propionate has already been demonstrated (James & Noyce, 1970) and we consider that the enhanced solubility in these solvents is due to association in this way. This idea is supported by the formation of isosbestic points (Cohen & Fischer, 1962) in both ester and conjugated ketone bands when the environments of the groups are changed stepwise from completely non-polar to the pure solvent. The simultaneous increase in the breadth of the bands further corroborates the postulate; this is a characteristic of associated species. These spectral modifications are shown in Fig. 2.

With aromatic solvents, specific interactions again occur between solute and solvent since isosbestic points are formed. The carbonyl vibrational bands are modified slightly (Fig. 3) with a smaller increase in bandwidth and a lower value of $\Delta\nu_{C:O}$ than in the halogenated aliphatic solvents, thus indicating that the interaction is weaker. It therefore follows that the solubilities of testosterone propionate in these solvents should be lower than in the first group, and this is borne out by the experimental results.

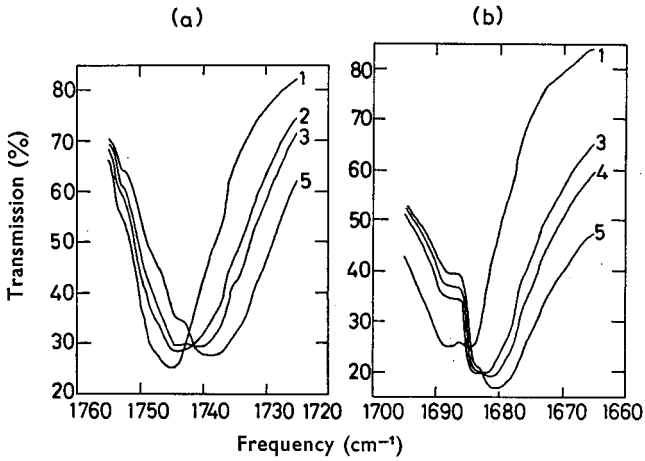

FIG. 2. Carbonyl stretching bands of (a) 17β-ester group, and (b) Δ^4-3-ketone group in *trans*-1,2-dichloroethylene-cyclohexane solvent systems. Molar ratio *trans*-1,2-dichloroethylene–testosterone propionate. 1. 0 (pure cyclohexane solvent). 2. 10·3. 3. 15·5. 4. 20·6. 5. 30·9.

Since the π-electron cloud of an aromatic compound is the probable area of interaction, hydrogen bonding is unlikely as both the π-cloud and the carbonyl oxygen are proton accepting. Laszlo & Williams (1966) and Williams & Wilson (1966), in their nuclear magnetic resonance studies of steroids in benzene and toluene, calculated that a collision complex in which the plane of the aromatic solvent was at right angles to that of the steroid, could account for their observed shifts. This mode of interaction has recently been questioned (Baker & Wilson, 1970). Our results indicate that interaction between the π-electrons and a positive centre in the steroid is unlikely because the shifts are in inverse order to the electron densities on the aromatic nuclei.

By the measurement of band widths it has previously been established that weak,

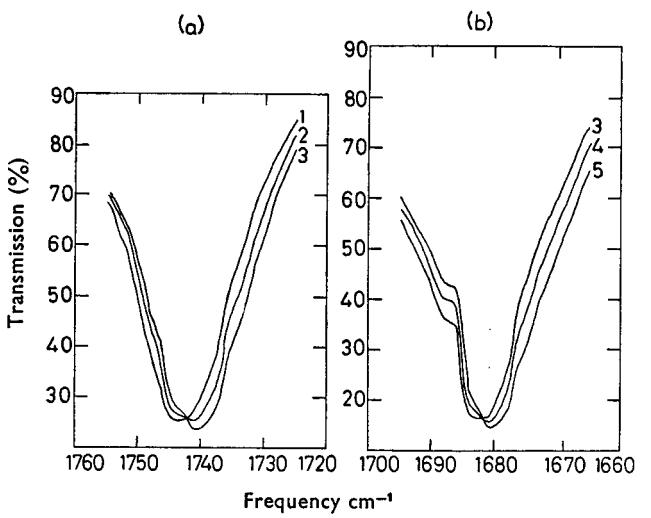

FIG. 3. Carbonyl stretching bands of (a) 17β-ester group and (b) Δ^4-3-ketone group in benzene-cyclohexane solvent systems. Molar ratio benzene–testosterone propionate. 1. 25·6. 2. 38·4. 3. 51·2. 4. 63·9. 5. 76·7.

but specific, interactions occur between carbonyl groups and carbon tetrachloride (Whetsel & Kagarise, 1962). The weak nature is further emphasized by the absence of isosbestic points (Fig. 4). In considering the characteristics of the carbonyl

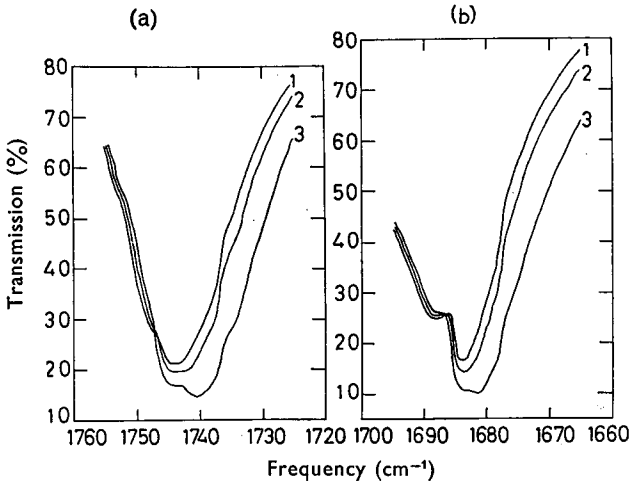

FIG. 4. Carbonyl stretching bands of (a) 17β-ester group and (b) Δ^4-3-ketone group in carbon tetrachloride–cyclohexane solvent systems. Molar ratio carbon tetrachloride–testosterone propionate. 1. 19·5. 2. 26·0. 3. 39·0.

vibrations in carbon disulphide, we assume that similar forces are involved to those in carbon tetrachloride, although in accordance with the suggestions of Caldow & Thomson (1960) bulk dielectric effects may contribute to the change in $\nu_{C:O}$ in moving from carbon disulphide to carbon tetrachloride.

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