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Polymorphism of auranofin

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Summary

Two forms of auranofin, designated as A and B, have been identified. These two forms are identical in composition and differ only in their crystalline morphology. Contrary to usual expectations, form A, having the lower melting temperature, also has the lower apparent equilibrium solubility. DSC and heat of solution measurements show that form A, although lower melting is the more stable by 3 kcal/mol in terms of the energy required to break up the crystal lattice. This apparent anomaly is rationalized in terms of greater cooperativity of interaction between molecules of A in the crystal lattice, although the strength of the individual interactions is weaker as evidenced by the lower melting point.

Introduction

Auranofin (5-triethylphosphine gold-2,3,4,6-tetra-o-acetyl-l-thio-β-D-glucopyranoside) (I) has been shown (Finkelstein, 1976; Berglof, 1978), to be clinically effective in the treatment of rheumatoid arthritis. This compound is currently undergoing extensive clinical trials. Two distinctly different crystalline modifications of auranofin have been identified by Razi et al. (1983) designated as forms A and B.

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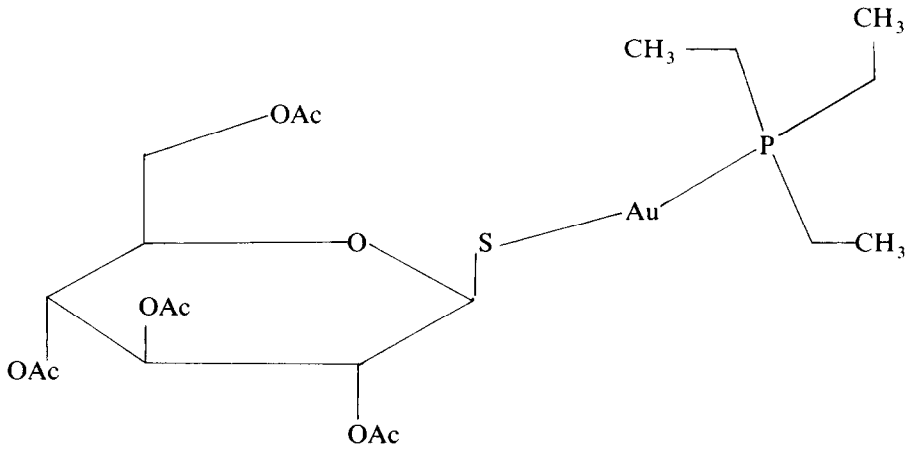

(I)

These forms differ considerably in their rates of dissolution and apparent equilibrium solubility characteristics. It is the purpose of this study to characterize these two forms with respect to their physicochemical properties and to determine their relative stability by measuring the energy difference between them.

Experimental

Materials

Auranofin, forms A and B (SK&F), (99.5% pure by HPLC analysis) were used as received. Water content for both forms was 1.7% by Karl Fisher titration. Further drying was not attempted in order to avoid morphology changes due to harsh drying conditions. β-D – Thioglucose tetraacetate was obtained from Aldrich Chemicals and was used as received. All other reagents and solvents were reagent grade.

Dissolution studies

300 mg of auranofin, forms A and B, previously passed through an 80-mesh screen, was added to 200 ml of a 25% aqueous solution of polyethylene glycol 200 equilibrated at 37°C with stirring at 200 rpm in a 250 ml thermostatically controlled dissolution vessel. 5-ml aliquot samples filtered through a 0.45 μm Millipore filter were withdrawn at 2, 4, 6, 8, 10, 20, 30, 45, 60, 90 and 120 min, respectively. 5 ml of the dissolution medium was added to the dissolution vessel after each sampling period to maintain a constant volume. The dissolution vessel containing form B was seeded with approximately 2 mg of form A after 120 min. Stirring was continued for an additional 1320 min after which a 5-ml aliquot sample, filtered as previously described, was withdrawn. The samples were analyzed by a high-pressure liquid chromatographic procedure, using a μBondapak C18 reversed-phase column with methanol and aqueous 0.01 M sodium dihydrogen phosphate (60 : 40 v/v) as the

mobile phase. Detection was by UV absorption at 240 nm. The relative standard deviation of the method is ±1.1% with an average recovery of 101%.

Differential scanning calorimetry (DSC)

DSC thermograms were obtained using a Perkin Elmer DSC-2 differential scanning calorimeter with a Model 3500 data station (Perkin Elmer, Norwalk, CT). Samples of approximately 3 mg were weighed and sealed into aluminum DSC sample pans. Thermograms were measured from 300 to 450°K at a heating rate of 5, 10 and 20°/min.

Solution calorimetry

Heats of solution of the two forms of auranofin were measured at 25°C in 95% ethanol and in dimethylformamide using a Tronac 450 (Tronac, Orem, UT) solution calorimeter. Samples of approximately 200 mg were weighed into 1 ml glass sample bulbs which were sealed with a microflame torch (Microflame, Minneapolis, MN). The sample bulbs are sufficiently thin so that no measurable heat effect is observed due to the breaking of the glass. The heats of solution were measured by breaking the sample bulbs in the reaction vessel containing 50.0 ml of solvent. The system was calibrated electrically by passing a measured current through the calibration heater for a measured length of time such that the calibration energy was approximately equal to the heat absorbed in the heat of solution measurement. The time vs temperature history of the reaction and calibration periods was monitored with a Linear Model 1801 stripchart recorder (Linear Instruments, Reno, NV). Heats of solution were calculated as described by Eataugh et al. (1974) The accuracy and validity of the method was checked periodically by measuring the heat of solution of tromethamine (THAM, tris-hydroxymethyl aminomethane) in 0.1 M hydrochloric acid. The values agreed in all cases within 1% of the accepted literature value of −7.115 kcal/mol at 25°C.

Infrared spectroscopy (IR)

A Nicolet (Madison, WI) 6000 Fourier transform infrared spectrometer equipped with a liquid nitrogen cooled mercury cadmium telluride (MCT) detector was used for all the infrared studies. Solids samples were run as KBr pellets having concentrations of 3 mg of sample to 200 mg of potassium bromide (KBr). Solution infrared work was accomplished using Irtran-2 (ZnS) transmission windows supplied by Wilmad Glass (Buena, NJ). A 0.1 mm pathlength was used for all solution measurements.

Results and Discussion

The dissolution profiles for forms A and B in 25% polyethylene glycol 200 are given in Fig. 1. Form B is more than twice as soluble as form A, and the initial rate of dissolution of form B is also more rapid. Seeding form B with form A does not cause interconversion, suggesting that form B is relatively 'stable'. In spite of the

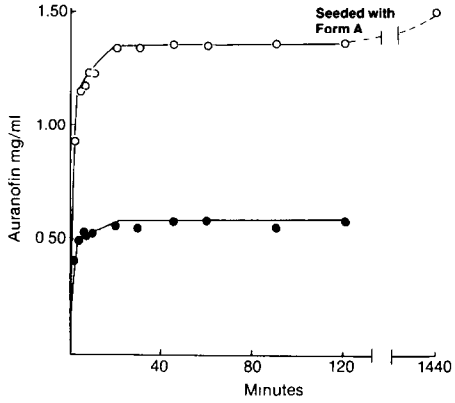

Fig. 1. Dissolution behavior of auranofin, Form. A (●) and Form B (○)

relative 'stability' of form B in the presence of form A, the higher solubility form is thermodynamically unstable relative to form A and may convert to that form given sufficient time.

DSC thermograms, normalized and adjusted to the same baseline, are given in Fig. 2, and the melting points and heats of fusion calculated from these data are given in Table 1. An unusual aspect of these data is the observation that the *lower* melting form A is the form having the lower solubility. It is usually expected, that

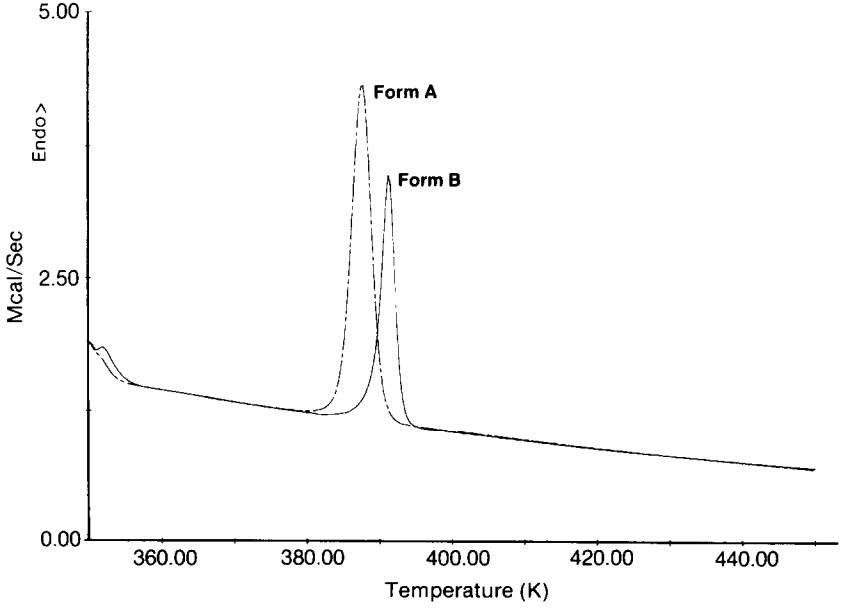

Fig. 2. DSC thermograms of auranofin.

TABLE 1

HEATS OF FUSION AND HEATS OF SOLUTION OF AURANOFIN POLYMORPHS

Heats of fusion (from DSC)		
	ΔH_F (kcal/mol)	m.p. (°K)
Form A	9.04	385
Form B	5.85	389
$\Delta H_{T(A \rightarrow B)}$	9.04–5.85 = 3.20 kcal/mol	
Heats of solution in 95% ethanol [a,b]		
	ΔH_s (kcal/mol)	
Form A	12.42 ± 0.07	
Form B	9.52 ± 0.04	
$\Delta H_{T(A \rightarrow B)}$	12.42–9.52 = 2.90 kcal/mol	
Heats of solution in dimethylformamide [a,b]		
	ΔH_s (kcal/mol)	
Form A	5.57 ± 0.13	
Form B	2.72 ± 0.01	
$\Delta H_{T(A \rightarrow B)}$	5.57–2.72 = 2.85 kcal/mol	

[a] Heats of solution were not corrected to infinite dilution. In all cases, the final concentration of drug was approximately 6×10^{-3} M. The small correction to infinite dilution is cancelled in the calculation of ΔH_T.

[b] The water content of forms A and B is expected to have a small effect on the absolute values of ΔH_s. Since the water content of the two forms is identical, however, the difference between heats of solution ΔH_T will not be significantly affected.

the lower melting form will be the more energetic species which would result in faster dissolution and greater initial solubility (Shefter, 1981). The DSC thermogram also shows, however, that the lower melting form A has the larger peak area and therefore the larger heat of fusion (Table 1). The form which is the high energy form with respect to melting temperature, form A, is the low energy (more stable) form with respect to heat of fusion.

The difference between the heats of fusion of the two forms is approximately equal to the heat of transition, ΔH_T of form A to form B:

$$\Delta H_T = \Delta H_F^A - \Delta H_F^B \quad (1)$$

where ΔH_F^A and ΔH_F^B are the heats of fusion of forms A and B, respectively.

The value of ΔH_T so obtained, 3.20 kcal/mol, is subject to corrections for the temperature differences at the melting points, and the difference in heat capacities of the liquid and solid drugs.

Heats of solution of approximately 200 mg of drug substance in 50 ml of solvent are also given in Table 1. The differences between the heats of solution of the two forms in a given solvent are equal to the heats of transition between them:

$$\Delta H_T = \Delta H_S^A - \Delta H_S^B \quad (2)$$

As expected for chemically identical forms differing only in their crystal lattice energy, the heats of transitions obtained in this way (Table 1) are independent of the solvent used for the heat of solution measurements. The good agreement between heats of transition obtained by DSC (3.2 kcal/mol) and those obtained from heats of solution (2.90 and 2.85 kcal/mol) suggests that the corrections to the heats of fusion, due to heat capacity and temperature differences are small. In both cases, these results confirm that form A is more stable (lower energy) than form B with respect to crystal lattice energy differences.

Auranofin polymorphs are unusual in that the lower melting form has the greater stability as measured by enthalpy of fusion and enthalpy of solution. Furthermore, the lower melting species has the lower solubility and lower dissolution rate. Enantiotropic systems in which the lower melting polymorph has the lower solubility have been previously reported (Haleblian and McCrone, 1969; Burger, 1975) and have been well characterized. Auranofin polymorphs are unusual in that there is no interconversion between forms even on heating to the melting point at various rates (5°C/min to 20°C/min). The solubility characteristics appear to be governed by energy differences as measured by ΔH_T. These phenomena would suggest that in the more stable form a cooperative interaction exists between neighboring molecules involving many weak bonds whereas fewer, but stronger, bonds are involved in the interaction between molecules in the less stable form.

In the case of auranofin polymorphs, it may be suggested that the lower melting form is stacked in such a way in the crystal lattice that the acetyl groups cooperatively interact by dipole–dipole interaction. This mode of interaction is illustrated schematically in Fig. 3A. In the higher energy and higher melting form the molecules interact more strongly, hence the higher melting temperature, but in a less cooperative fashion such that not as much energy is required to disrupt the lattice. Crystal structure data are only available for form A (Hill and Sutton, 1980). The superposi-

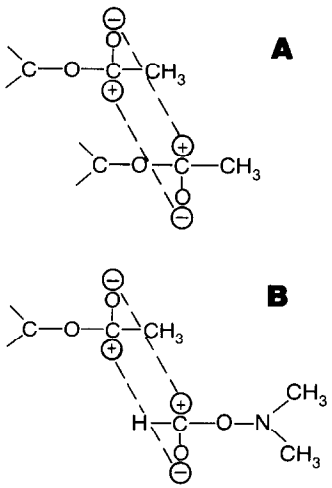

Fig. 3. A: suggested mode of interaction between auranofin molecules in the crystal lattice of the more stable form A. B: suggested mode of solvation of auranofin by dimethylformamide.

tion of the glucopyranose rings in the unit cell lends support to the suggestion that the lattice is stabilized by dipole–dipole interactions between carbonyl groups. Crystal structure data for form B would also be required to confirm this suggestion. Since enthalpies of solution were measured in two solvents, ethanol and dimethylformamide, it is possible to calculate the enthalpy change associated with the process of transferring auranofin from one solvent to another (Eqn. 3):

$$\Delta H_{T(EtOH \rightarrow DMF)} = \Delta H_{S(DMF)} - \Delta H_{S(EtOH)} \quad (3)$$

where $\Delta H_{T(EtOH \rightarrow DMF)}$ is the enthalpy change for transferring auranofin from

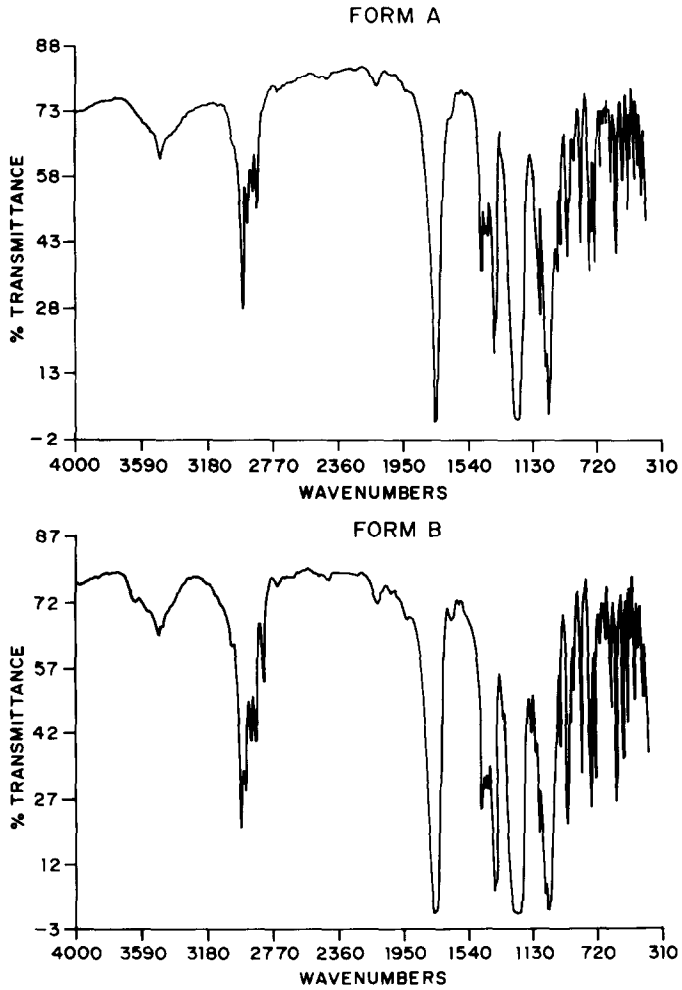

Fig. 4. FT-IR spectra of auranofin, form A and form B.

ethanol to dimethylformamide. These values are expected to be independent of morphology since crystal lattice energy differences are cancelled. The results, -6.96 kcal/mol for form A and -6.80 kcal/mol for form B, confirm this expectation within the experimental error. This agreement also confirms the validity of the assumption that forms A and B are identical chemically and differ only in morphology. The negative value for the heat transfer to DMF suggests that in this solvent the auranofin molecule is more strongly solvated than in EtOH. Likely sites for the solvation interactions are the ester groups on the glucopyranose ring. In order to verify this conclusion, heats of solution of β-D-thioglucose tetraacetate were also measured in 95% ethanol and dimethylformamide. Values of 9.43 ± 0.16 kcal/mol and 3.25 ± 0.27 kcal/mol were obtained in ethanol and dimethylformamide, respectively. Accordingly, the enthalpy of transfer for β-D-thioglucose [$\Delta H_{T(EtOH \rightarrow DMF)}$] is -6.18 kcal/mol which is in reasonable agreement with the value for auranofin.

Interaction between polarized acetyl groups on the glucopyranose ring and dimethylformamide is depicted schematically in Fig. 3B. The observation that both auranofin and β-D-thioglucose react similarly with dimethylformamide provides further justification for this suggestion. Further evidence for this suggestion is provided by the IR data.

The infrared spectra of polymorphic forms A and B (Fig. 4) of auranofin differ in a number of structurally informative areas. The primary regions of difference correspond to O–H stretching, C–H stretching, C = O stretching, C–H deformation and P–C stretching vibrations. The most structurally diagnostic of these areas is the carbonyl region from 1825 to 1675 cm^{-1} which corresponds to auranofin's acetate functionalities.

Fig. 5 represents infrared spectra of the carbonyl regions of auranofin forms A and B. The band at 1751 cm^{-1} for form A is seen to shift to 1755 cm^{-1} for form B.

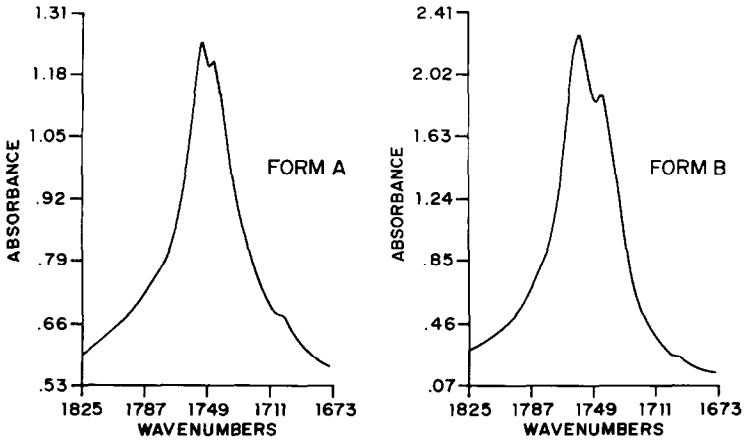

Fig. 5. FT-IR carbonyl stretching region, form A and form B.

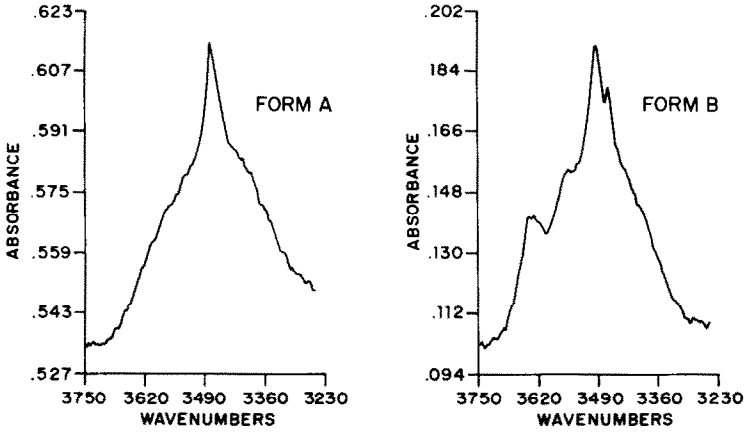

Fig. 6. FT-IR O–H stretching region, form A and form B.

A similar shift may be observed as auranofin is diluted in chloroform solution. At a concentration of 100 mg/ml, a strong carbonyl band is observed at 1736 cm^{-1} with weaker bands at higher frequencies. As chloroform is added and the auranofin concentration is reduced, dissociation of dipole–dipole interaction is believed to occur. This results in a progressive shift of the carbonyls to higher frequencies in the infrared. At approximately 4 mg/ml, total disruption of interactions has occurred and all carbonyls absorb in the infrared at 1750 cm^{-1}.

Bellamy (1975) has reported that such increases in carbonyl IR absorption frequencies can be the result of decreases in the polarity of carbonyl functional groups. Acetone is an example of this (Cross and Jones, 1969). In the liquid phase, acetone associates by means of carbonyl dipole–dipole interactions. Carbonyl absorption bands occur at 1718 cm^{-1}. In the vapor phase (where no intermolecular interactions occur), the carbonyl IR absorption frequency increases to 1742 cm^{-1}.

Since both solution and solid auranofin show increases in carbonyl IR absorption frequencies with interaction loss, it seems likely that auranofin crystalline form A molecules are held together by multiple intermolecular dipole–dipole interactions (Fig. 3) in a manner analogous to acetone. This interaction appears to be absent or present to a lesser degree in form B.

Important structural differences are also evident in the O–H stretching region from 3750 to 3230 cm^{-1} (Fig. 6). These bands are due to water present in both forms of auranofin. The change in shape and shift to higher frequency in going from form A to B may represent enhanced intermolecular hydrogen bonding interactions for form B, which would explain the higher melting point of this polymorph. These interactions, though stronger than the dipole–dipole carbonyl interactions, would involve fewer molecules. Accordingly, the greater stability of form A as measured calorimetrically may be attributed to enhanced cooperative interaction between many acetate groups (Fig. 3), whereas the higher melting temperature of form B suggests stronger (but fewer) hydrogen bonding interactions.

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