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Stereochemical Aspects of the Molecular Pharmaceutics of Ibuprofen

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Abstract—Thermal analysis, thermodynamics of solution and molecular modelling of (+)-ibuprofen and (±)-ibuprofen gave information on how heterochiral or homochiral interactions would affect the processing of ibuprofen. The study confirmed that (±)-ibuprofen exists as a true racemate with a 10% eutectic pure enantiomer composition. Both the racemate and the (+)-isomer crystal unit cells include four molecules and crystallize in the $P2_{1/c}$ and $P2_1$ space groups, respectively. Thus the intermolecular forces were different in each crystal. As a consequence the (+)-enantiomer lattice was more fragile but only slightly more soluble than the racemate in aqueous media. The solid-state structure contributions to solubility were different for the two crystals ($\Delta H(+) = 51{\cdot}1$ and $\Delta H(\pm) = 32{\cdot}2$ kJ mol^{-1}) but the standard free energies of the solutions were comparable for both compounds.

It is generally recognized that (+)-ibuprofen is the enantiomer of ibuprofen inhibiting the prostaglandin synthetase (Adams et al 1976; Campbell 1990). The stereochemistry and conformation of this isomer are important for the interaction with the cell receptors responsible for the therapeutic anti-inflammatory activity. Another consequence of chirality could be the difference in the crystal habits of the two separate isomers and the racemate. We now report a continuation of our studies in this area (Romero & Rhodes 1991).

We have previously reported higher solubility, lower melting point and smaller intrinsic dissolution rates for the (+)-isomer compared with the racemate (Romero & Rhodes 1991). The combination of tests used in this study is, we believe, essential when investigating a chiral compound or an optically pure isomer. For example, the thermal behaviour of sobrerol and diastereoisomers was reported (Bettinetti et al 1989) and the crystal structures of cytostatic agents (stereoisomers and mixtures) were elucidated (Hempel et al 1982), both in support of formulation efforts. In another study the thermodynamic functions of non-steroidal anti-inflammatory agents in solution, including ibuprofen, have been thoroughly studied (Yalkowsky & Valvani 1980) to determine the effect of the solid state structures on solubility. The physical characteristics can be related to the molecular packing of the crystals under study (Forni et al 1984).

The combination of these tests and the comparative analysis is a unique approach to the formulation of ibuprofen enantiomers, largely overlooked before stereospecific synthesis became economically viable.

Materials and Methods

Materials

Racemic and (+)-ibuprofen were supplied by the Ethyl Corporation (Baton Rouge, LA, USA). Methanol from the Fisher Scientific Co. was used for ibuprofen recrystallization and was of analytical grade. Potassium phosphate monobasic and sodium hydroxide were obtained from Malinckrodt and J. T. Baker, respectively.

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Methods

Thermal analysis. Ibuprofen mixtures containing various enantiomeric proportions were prepared by slow recrystallization at 5·9°C from methanol and after melting. Thermal analyses were performed on (+)-ibuprofen, (−)-ibuprofen, (±)-ibuprofen and mixtures using a differential scanning calorimeter (DSC) from Perkin Elmer, series 7. The heating rate was set at 5°C min^{-1} under nitrogen flushing. Thermal endotherms were integrated to obtain thermodynamic functions used for the phase-diagrams. Theoretical solid-liquid equilibrium curves were drawn using the Prigogine-Defay equation (eqn 1) for the racemate completely dissolved in the melt and the Schroeder Van-Laar equation (eqn 2) for the simple eutectic formation (Jacques et al 1981). Thus, eutectic temperature and compositions could be determined:

$$\mathrm{Ln}4x(1-x) = 2\Delta H^{(\pm)}/(R^*(1/T^{(\pm)} - 1/T^f)) \quad (1)$$

$$\mathrm{Ln}x = \Delta H^s/(R^*(1/T^{(+)} - 1/T^f)) \quad (2)$$

where x is the mole fraction of the more abundant enantiomer in the mixture, whose melting ends at T^f (K); $\Delta H^{(+)}$ and $\Delta H^{(\pm)}$ are the enthalpy of fusion of the pure (+)-isomer and the racemic form, respectively; $T^{(+)}$ and $T^{(\pm)}$ are the corresponding melting points and R is the gas constant at 1·987 cal mol^{-1} K^{-1}.

Crystal analysis. Single-crystal X-ray diffraction was performed on small crystals of (+)-ibuprofen from the bulk compound. Reflection data was obtained from Ethyl Corporation and processed on a molecular modelling program (Shelxtl). Crystal data are given in Table 1. The structure was solved in the space group $P2_{1/c}$. Analysis of the unit cell allowed the identification of the molecular packing and hydrogen bonds network within the monoclinic crystal. Similar information on the racemate was obtained from the literature (McConnell 1974) and compared with the newly obtained molecular packing data of the (+)-enantiomer.

Solubility. Excess amounts of both compounds were suspended in 0·05 M aqueous buffered solutions at pH 1·3. At this pH, the drug is essentially un-ionized since its pK_a is in the range 4·6–5·2. Screw cap vials were rotated on a

Table 1. Crystal data for (+)-ibuprofen and (±)-ibuprofen.

	(+)-Ibuprofen	(±)-Ibuprofen
Formula	$C_{13}H_{18}O_2$	$C_{13}H_{18}O_2$
Mol. wt	206·3	206·3
Crystal system	monoclinic	monoclinic
Space group	$P2_{1/c}$	$P2_1$
a(A)	12·46	14·67
b(A)	8·03	7·88
c(A)	13·53	10·73
α(A)	—	—
β(A)	112·95	99·3
No. of molecules in the cell	4	4
Density (g cm^{-3})	1·098	
CuK_α radiation		

Labshaker for 24 h at temperatures ranging from 25 to 52°C in walk-in ovens. Quantitative analysis was performed using UV spectrophotometry at selected wavelengths (220 and 264 nm). The variation of the solubility expressed in x^w (mole fraction in the solution) can be integrated to:

$$\text{Ln } x^w = \text{constant} + (-\Delta H^\circ/R)(1/T) \quad (3)$$

and experimental data can be analysed by plotting the natural log of the solubility vs 1/T. The free energy of solubility at a given temperature can be obtained from:

$$\Delta G^\circ = -RT \cdot \text{Ln } x^w \quad (4)$$

and the entropy of solution is derived from the third law of thermodynamics:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (5)$$

All thermodynamic parameters were analysed to compare the racemate and (+)-ibuprofen. The contribution of ibuprofen stereochemistry (solid-state structures) to solubility, was investigated. In a recent study, thermodynamic functions were used to predict and separate the roles of solid-state structures from solute-solvent interactions in promoting the solubility of a solid nonelectrolyte (Hempel et al 1982).

Results and Discussion

Thermal behaviour

Thermodynamic functions are reported in Table 2. Melting parameters (Tm and ΔH) obtained from the thermograms in Figs 1 and 2, were used in equations 1 and 2 to obtain the phase-diagram in Fig. 3 (Yalkowsky & Valvani 1980). Experimental data were in good agreement with the theoretical lines indicating the fusion of the eutectic at about $T^{eu} = 321$ K and a eutectic composition of 10·0% on each

Table 2. Thermodynamic functions of melting and solubility.

Ibuprofen	(±)	(+)	(−)
Melting			
Tm Melting point (K)	349	327	327
ΔH Enthalpy (J mol^{-1})	25·5	17·9	17·9
ΔS Entropy (J $mol^{-1}K^{-1}$)	73·2	54·8	54·8
Solution			
ΔH (J mol^{-1})	32·2	51·5	—
ΔS (J $mol^{-1}K^{-1}$)	6·7	73·4	—
ΔG (J mol^{-1})	30·2	29·6	—

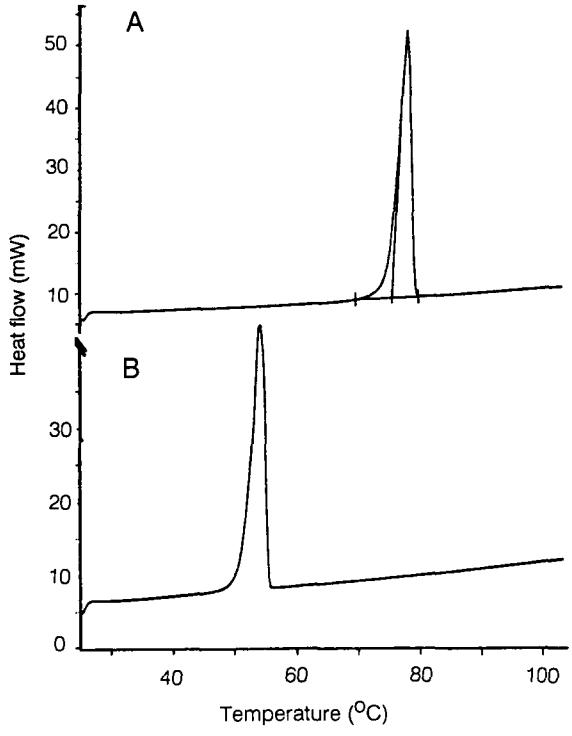

FIG. 1. Typical DSC endotherms. A. (±)-Ibuprofen. B. (+)-Ibuprofen.

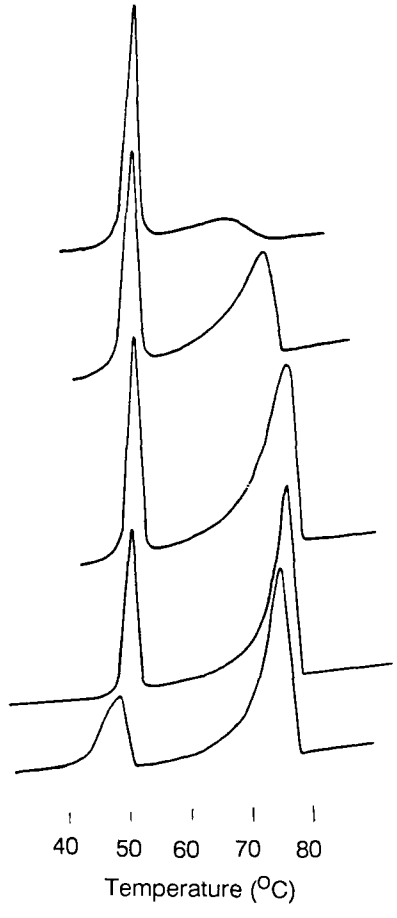

FIG. 2. DSC thermograms of ibuprofen. Different enantiomeric composition.

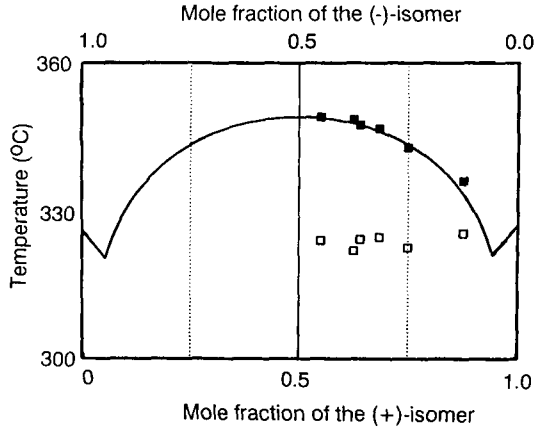

FIG. 3. Phase diagram of ibuprofen. Determination of enantiomeric composition.

side. A Peterson ratio (i) of 1·77 was calculated from equation 6 (Jacques et al 1981).

$$i = (Tm^{\pm} - Tm^{eu})/(Tm^{+} - Tm^{eu}) \quad (6)$$

where Tm^{eu} is the eutectic temperature as determined experimentally and from the phase diagram.

Although somewhat arbitrary in character, this ratio clearly indicated that ibuprofen has a strong tendency to crystallize as a true racemate. The melting point of either isomer was 20 to 22°C lower than that of the racemate and eutectics were very close to the edges of the diagram making any enantioselective resolution by crystallization impossible. The test of the Prigogine-Defay equation was performed and the straight line in Fig. 4 confirmed the model.

Crystal packing

Perspective drawings of the molecular packing in the crystals of (+)-ibuprofen are given in Fig. 5. (+)-Ibuprofen is more water-soluble than the racemate (Campbell 1990) and it is of interest to seek the basis for the differing solubilities or thermal behaviour in terms of intermolecular attraction. Although having the same number of molecules, (+)-ibuprofen crystals and racemate crystals have different unit cells (Fig. 5). The array of (+)-molecules involved in homochiral interactions probably spreads the mechanical stability/strength of the crystal (Fig. 6). The preferential molecular arrangement in the $P2_1$ plan exhibit some of the acid groups 'face-up' and others 'face-down' so that all the layers of molecules are interconnected with pairs of hydrogen bonds to carboxyl groups. Assuming that the top layer of the crystal is one, the crystal surface is different for the two compounds. Thus, in the case of (+)-ibuprofen there are more exposed carboxyls and less hydrophobic layers. There is a greater number of crystallographically independent molecules in the (+)-crystals and there are no obvious relationships between molecular packing in the lattice of racemate and enantiomers.

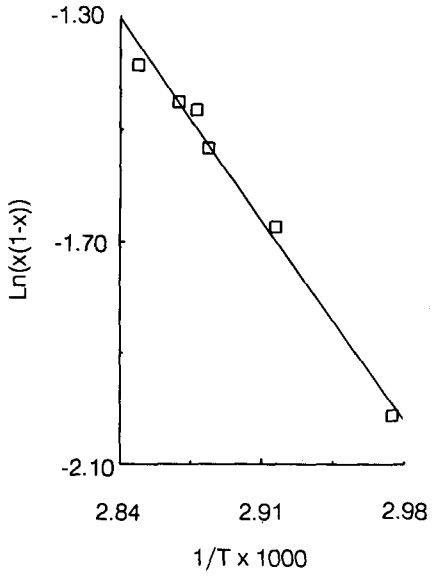

FIG. 4. Test of the Prigogine-Defay equation.

The structural data reflect different intermolecular environments. In order to pack together, molecules of the same chirality had to be flexed in order to meet the space requirements of the lattice. A qualitative measure was the superposition of two (+)-ibuprofen molecules involved in the same hydrogen bond which clearly demonstrates the torsion (Fig. 7).

Solubility

The solubility of crystalline solid is determined by the free energy changes from the solid state to a solution. As indicated in Table 2, ΔG° at 25°C is slightly higher for the racemate than for its (+)-isomer which may account for the differing solubilities. Similar conclusions could be drawn from the analysis of fusion parameters. The enthalpy and entropy contributions to water solubility as revealed by the thermodynamic functions in Table 2, are very different suggesting that solid-state structures are responsible for these differences.

Qualitatively and quantitatively, the intermolecular network of interactions in crystal unit cells of the racemate significantly exceeds that existing within cells of the pure enantiomer and can also reasonably account for the solubilities, thermal behaviour and further processing characteristics. The literature indicates that in some instances, when the melting point of pure stereoisomers is substantially lower than the racemate, the optical isomers are several fold more soluble than the corresponding racemate (Forni et al 1984; Romero & Rhodes 1991). In this case, the *S*(+)-isomer was only slightly more water soluble than (±)-ibuprofen. We attribute this phenomena to the molecular arrangement in the lattice of (+)-ibuprofen. Solid-state structure contributions (ΔH) to solubility were different between the (+)-isomer and the racemate. At pH 1·3 the entropy effect (ΔS) counterbalanced this effect and standard free energies were almost equivalent for the two crystals. These results confirmed the low specific surface area and the slow intrinsic dissolution rate of (+)-ibuprofen. In addition, the crystal lattice exhibited potentials for mechanical instability if perturbed by components of high hydrogen bonding affinities.

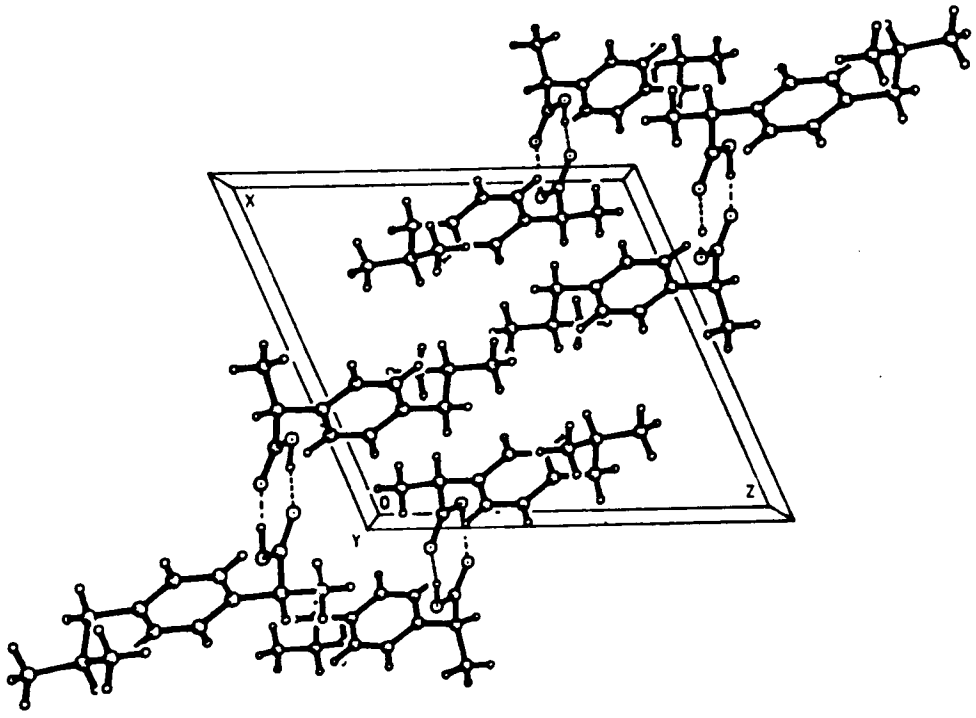

FIG. 5. Crystal unit cell of (+)-ibuprofen.

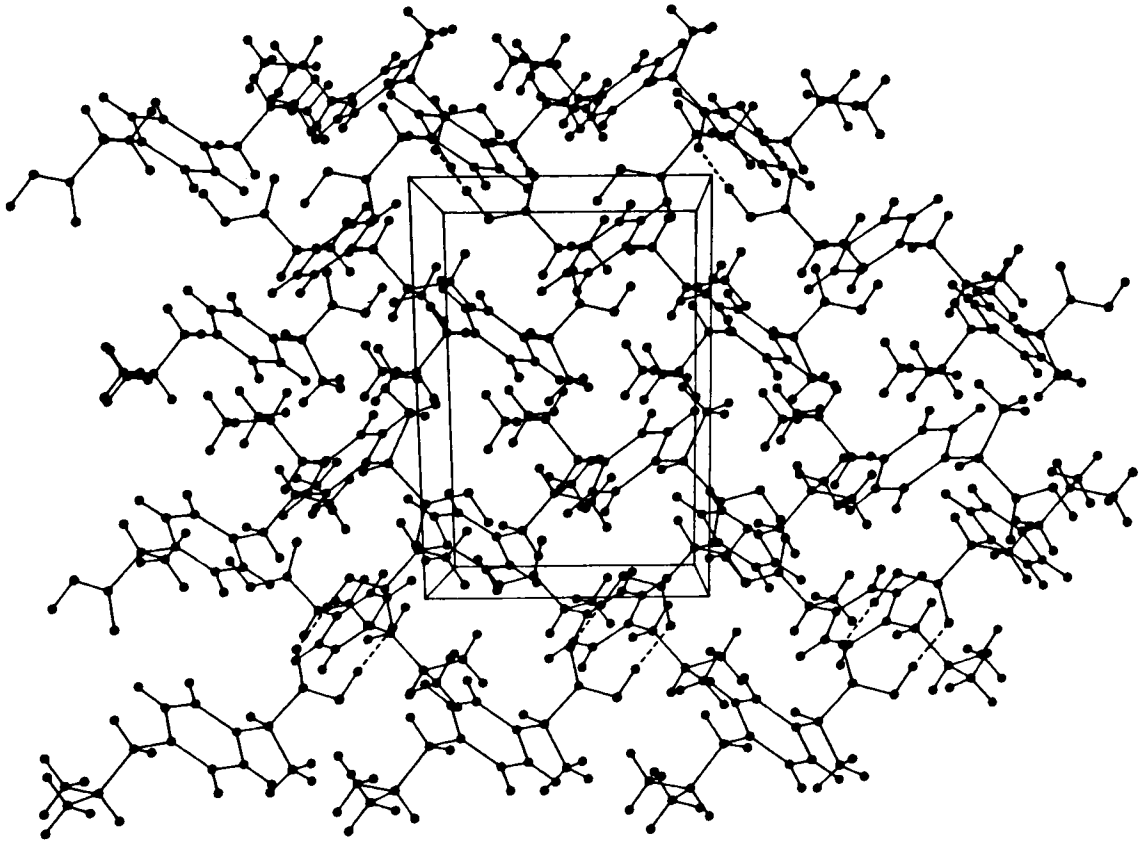

FIG. 6. Crystal lattice of (+)-ibuprofen.

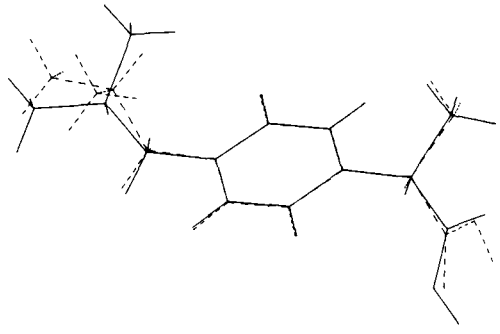

FIG. 7. Superposition of (+)-ibuprofen molecules involved in the same hydrogen bond.

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