CORRELATION BETWEEN THE THERMODYNAMICS OF AQUEOUS IMMERSION AND MOLECULAR STRUCTURE

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Determination of the Gibbs free energy (ΔGi), enthalpy (ΔHi) and entropy (ΔSi) changes upon immersion of powdered solids in water has been shown to provide a much greater understanding of the factors controlling the immersion process (Storey, 1985). From these thermodynamic parameters it is possible to conclude whether aqueous immersion is either entropically or enthalpically controlled. Moreover, if it were possible to quantitatively relate molecular structure to these thermodynamic parameters this would enable prediction of the relative ease of immersion of a compound based solely on its molecular structure. This could then be used as an aid in drug design.

The enthalpy change upon immersion into water for the imidazoles chosen for this structure-immersion correlation is dependent upon the number and strengths of hydrogen bonds broken and reformed during the immersion process. The strength of a hydrogen bond may qualitatively be related to the electronegativity of the atom involved in the bond or, on a quantitative basis, the electron density (ED) or the frontier electron density (FED) may be used. To compare FED of atoms in different molecules the FED must be normalised by dividing by the energy of the highest occupied molecular orbital of each molecule. The index so obtained is referred to as the superdelocalisability index (SI). Hence, the sum of the ED, FED or SI of all relevant hydrogen bonding atoms in each molecule may provide a correlation with the observed enthalpy change upon immersion. This does of course assume that all atoms involved in hydrogen bond formation with water molecules are equally available over the entire crystal surface. The computer-based molecular orbital (MO) theory "CNINDO" was used to compute the minimum energy conformations for each of the molecules and then the ED, FED and SI of all relevant hydrogen bonding atoms in each molecule.

Table 1. Collected data for imidazole (I), 2-methylimidazole (II), metronidazole (III), 2-methyl-5-nitroimidazole (IV), 4-nitroimidazole (V).

Compound	*ΔGi (Jm^{-2})	*ΔHi (Jm^{-2})	*ΔSi ($Jm^{-2}K^{-1}$)	Sum of ED	Sum of FED	Sum of SI
I	-0.37	44.3	0.150	0.440	5.32×10^{-2}	5.86×10^{-3}
II	-0.26	33.6	0.114	0.425	6.33×10^{-2}	7.03×10^{-3}
III	-0.30	4.04	0.015	1.366	8.86×10^{-2}	8.82×10^{-3}
IV	-0.24	2.81	0.010	1.072	9.94×10^{-2}	9.80×10^{-3}
V	-0.17	-0.21	0.0001	1.035	12.78×10^{-2}	12.47×10^{-3}

(*Storey,1985)

No correlation exists between ΔGi and any of the above three MO indices, nor between ΔHi or ΔSi and ED. However, linear relationships are found when either FED or SI are plotted against the natural logarithm of $(\Delta Hi)^2$ or ΔSi, correlation coefficients are 0.99 for $(\Delta Hi)^2$ and 0.93 for ΔSi. Thus for related imidazoles, calculation of FED or SI using molecular orbital theory will permit a calculation of ΔHi and ΔSi. ΔGi can then be calculated from ΔHi and ΔSi using the Gibbs equation, and from ΔGi the wettability of a particular compound may be deduced since the more negative ΔGi the greater the ease of immersion.

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