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STRUCTURE–ACTIVITY RELATIONSHIPS FOR SOLUBILITY AND WETTABILITY OF A NUMBER OF SUBSTITUTED BARBITURIC ACIDS

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ABSTRACT

Data taken from published work on the physical properties of substituted barbituric acids show that structure–activity relationships exist for the wetting and for the solubility of these powders. Wetting and solubility results of the powders do not fall in the same rank order; this is demonstrated by phenobarbitone which has a wettability intermediate between the barbituric acids with the hydrophilic four-carbon substituent and the hydrophobic five-carbon substituent (butobarbitone and pentobarbitone, respectively), but has a reported solubility lower than that of butobarbitone and pentobarbitone.

Compensation analysis of the wetting data shows a strong correlation with the results aligned in the perceived rank order of wettability. The compensation temperature is ~ 298 K. A strong correlation exists for the enthalpy–Gibbs function plot for the solubility data, revealing a surprising ordering of the compounds in a manner unrelated to their rank order of solubility.

INTRODUCTION

The rate at which a solid dissolves in an aqueous medium depends on its chemical nature. Two components are likely to be involved in controlling the rate of solution: the equilibrium solubility and the wettability of the powder. There are reports in the literature which describe variation in solubility as a

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function of structural variation. One such report is that by Yalkowsky et al. [1], who looked at an homologous series of alkyl aminobenzoates. The effect of adding a methylene group to the straight chain alkyl substituent resulted in a curious and still largely unexplained response. The solubility in hexane and silicone oil produced a linear rise until the substituent chain length was four carbons long, followed by a stepwise, rather than a linear, fall in solubility after this point. These results fit two parallel straight lines, one for the even carbon-chain lengths and one for the odd, presumably reflecting a crystal-packing phenomena. The graph of solubility in water as a function of carbon number had a linear fall until carbon four, followed by a second distinctly different linear portion; the explanation for the split is related to a change in crystal form after carbon four.

There are very few reports in the literature concerning the wetting of a variety of adsorbents (e.g. chemically related powders) by one adsorbate (e.g. water). The majority of published work concentrates on one adsorbent and a number of similar adsorbates. It is clear that the wettability of a powder will depend upon its physical history [2] and chemical nature. The effect of changes in the chemical nature of related powders on wettability has not been adequately described in the literature.

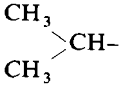
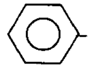
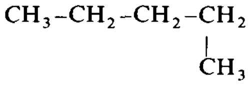
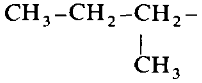
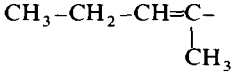
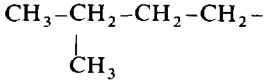
The purpose of this paper is to examine previously published data and to explore the possibility of the existence of structure–activity links for wetting and solubility of chemically related powders.

ORIGINS OF THE RESULTS

A thermodynamic assessment of the wetting of chemically related powders by water has recently been reported [3,4]. The powders studied were substituted barbituric acids but unfortunately they did not form a homologous series or have systematic variations in structure. These studies were of sound thermodynamic basis, not relying on indirect contact-angle measurements, and consequently, they provide the best source of results for use in this paper. Previous workers, by application of Young's equation [5], have used estimates of the contact angle theoretically formed by a liquid on a powder, in order to obtain the Gibbs function for the wetting process. Some of the theoretical and practical limitations and criticisms of the use of indirect contact-angle measurements for assessing the wetting of powders have recently been reported [6,7]. The four powders used in the wetting experiments were butobarbitone, phenobarbitone, pentobarbitone and amylobarbitone (for formulae see Table 1). Two methods were used to assess the thermodynamic parameters associated with the wetting of these powders. The first utilized a vacuum microbalance technique to monitor the adsorption of water vapour onto a reproducibly desorbed powder surface [3]. An equilibrium constant K was defined for adsorption and the Gibbs function

TABLE 1

The trivial names, proper names and formulae of the substituent on position 5 of the barbituric acid ring

Trivial name	Proper name (suffix: barbituric acid)	R5 group
1 Barbitone	5,5-Diethyl	CH_3-CH_2-
2 Butobarbitone	5-Ethyl-5-butyl	$CH_3-CH_2-CH_2-CH_2-$
3 Probarbitone	5-Ethyl-5-isopropyl	
4 Phenobarbitone	5-Ethyl-5-phenyl	
5 Pentobarbitone	5-Ethyl-5-(1-methyl butyl)-	 $CH_3-CH_2-CH_2-\underset{CH_3}{\underset{\vert}{CH_2}}$
6 Butabarbitone	5-Ethyl-5-(1-methyl propyl)-	 $CH_3-CH_2-\underset{CH_3}{\underset{\vert}{CH_2}}-$
7 Vinbarbitone	5-Ethyl-5-(1-methyl-1-butenyl)-	 $CH_3-CH_2-CH{=}\underset{CH_3}{\underset{\vert}{C}}-$
8 Amylobarbitone	5-Ethyl-5-(3-methyl-butyl)-	 $CH_3-\underset{CH_3}{\underset{\vert}{CH_2}}-CH_2-CH_2-$

for adsorption was calculated ($\Delta_{ads}G = -RT \ln K$, where R is the gas constant and T is the absolute temperature). Experiments were undertaken at a number of temperatures and the isosteric enthalpy of adsorption $\Delta_{ads}H_{iso}$ was obtained by a van't Hoff approach; the isosteric term $\Delta_{ads}S_{iso}$ was subsequently computed. The second method [4] relied on the vacuum microbalance to provide the data necessary to define the Gibbs function (via the equilibrium constant), but a microcalorimetric technique was used to measure the enthalpy of adsorption $\Delta_{ads}H_{cal}$ directly. The results were calculated from the power–time curve produced from the microcalorimeter and corrected to relate to the power output per mole of adsorbed water into unit weight of powder (i.e. a combination of data from the two techniques). The entropy of adsorption $\Delta_{ads}S_{cal}$ was computed. The interaction between powder and water (vapour), rather than water (liquid), was studied in these wetting experiments. This is justified on the basis that it is the first monolayer of adsorbed water that is most strongly indicative of the powder–water interaction, with multilayer adsorption being analogous to condensation (in line with the BET theory [8]) and subsequent immersion in liquid water only resulting in a rearrangement of the outer water molecules to fit with the structure of bulk water.

Data on the solubility of substituted barbituric acids (including those used in the wetting measurements) are available in the literature [9,10]. Wang and Paruta [9,10] have reported the solubility of ten such compounds in buffer at the pK_a of the compounds (50% in the salt form and 50% in the acid form), and at three pH units below the pK_a (termed pK_u) where only the undissociated acid form of the powder would exist. Eight of the powders studied had substituents on position five of the barbituric acid ring; these are considered here. Solubilities were measured between 298 and 313 K and the enthalpy and entropy of solution ($\Delta_{sol}H$ and $\Delta_{sol}S$) were obtained by use of a van't Hoff approach (from the gradient and intercept of the ln(solubility) versus reciprocal temperature graph, respectively). The Gibbs function $\Delta_{sol}G$ was then calculated.

DISCUSSION

Two sets of thermodynamic functions exist for the wetting of the powders: isosteric and calorimetric (Table 2). Clear differences can be noted between the isosteric and calorimetric data. With all four powders tested, the weight of water adsorbed was very similar, likewise the variation of weight of uptake with temperature was similar for each powder. Consequently, the van't Hoff analysis showed little difference between the adsorption properties of the four powders. The calorimetric data showed, however, that despite the similar uptake of water (with respect to weight) the enthalpy change upon adsorption was significantly different between the four powders. It can be concluded that the strength of the binding forces of the water molecules are different for each of the powders. This suggests a different mechanism of wetting for each of the powders and shows the advantage of direct calorimetric measurements over indirect (isosteric) assessments of the enthalpy of adsorption. The powders studied have a perceived wettability in the order amylobarbitone, pentobarbitone, phenobarbitone and butobarbi-

TABLE 2

The thermodynamic functions of adsorption at 298 K

Powder	Quantity adsorbed water (mg per 10.000 mg)	$\Delta_{ads}H_{cal}$ (kJ mol^{-1})	$\Delta_{ads}G$ (kJ mol^{-1})	$\Delta_{ads}S_{cal}$ (J mol^{-1} K^{-1})	$\Delta_{ads}H_{iso}$ (kJ mol^{-1})	$\Delta_{ads}S_{iso}$ (kJ mol^{-1} K^{-1})
Amylobarbitone	0.080	−25.5	38.4	−214.4	−66.8	−353.0
Pentobarbitone	0.080	−12.7	38.4	−171.5	−67.5	−355.4
Phenobarbitone	0.074	−8.1	38.6	−156.7	−65.2	−348.3
Butobarbitone	0.080	−4.5	38.4	−144.0	−61.4	−334.9

TABLE 3

Solution thermodynamics for substituted barbituric acids at their pK_a and at three pH units below their pK_a (pK_u), recalculated from data in ref. 10

Powder	$\Delta_{sol}H$ (kJ mol^{-1})		$\Delta_{sol}S$ (J mol^{-1} K^{-1})		$\Delta_{sol}G$ (kJ mol^{-1})	
	pK_u	pK_a	pK_u	pK_a	pK_u	pK_a
Barbitone	19.4	14.8	6.4	7.5	17.4	12.5
Butobarbitone	15.6	13.9	3.3	7.5	14.5	11.6
Probarbitone	21.9	20.9	1.7	3.4	21.4	19.9
Phenobarbitone	30.9	27.9	1.4	2.6	30.5	19.4
Pentobarbitone	21.1	23.7	0.8	2.0	20.8	23.1
Butabarbitone	28.3	25.3	0.9	1.9	27.9	24.7
Vinbarbitone	25.5	24.5	3.9	2.6	24.3	23.7
Amylobarbitone	20.9	14.6	5.3	4.0	19.2	13.3

tone, going from most hydrophobic to most hydrophilic [6]. The calorimetric enthalpy of adsorption is inversely proportional to the rank order of wetting behaviour, with the most hydrophobic having the largest negative enthalpy of adsorption; whereas, the calorimetric entropy of adsorption exhibits a direct correlation with the powders' wetting nature. In all cases, the adsorption is entropically hindered, but the adsorption onto the most hydrophobic powder produces the most ordered system. A mechanism for this adsorption has been proposed whereby the prevalence of powder–water binding sites controls the process; on hydrophobic powders it is assumed that few powder–water bonds form, and that the weight of adsorbed water is arranged as entropically hindered 'droplets' anchored to the powder surface by comparatively few water molecules. For hydrophilic powders, water binding sites abound, allowing (near) monolayer coverage and subsequent multilayers, an arrangement which is envisaged as being less ordered than the 'droplets' formed on the hydrophobic powders. This mechanism, together with supporting kinetic evidence, is described in more detail elsewhere [4].

To study the possibility of structure–activity relationships, compensation testing has been employed. Krug [11,12] has reported that in circumstances where the entropy term is determined directly from the enthalpy term, there is a possibility of a false correlation being observed for enthalpy–entropy compensation plots. Consequently, the use of enthalpy–Gibbs function plots are favoured to demonstrate the existence of chemical causality in such systems. For the solubility data plots of the enthalpy of solution as a function of the Gibbs function of solution, straight lines are obtained with correlation coefficients of 0.999 (pK_u data) and 0.997 (pK_a data) (Figs. 1 and 2). With the wetting data, the Gibbs function was essentially identical for each powder, and therefore, the plots were for enthalpy–entropy com-

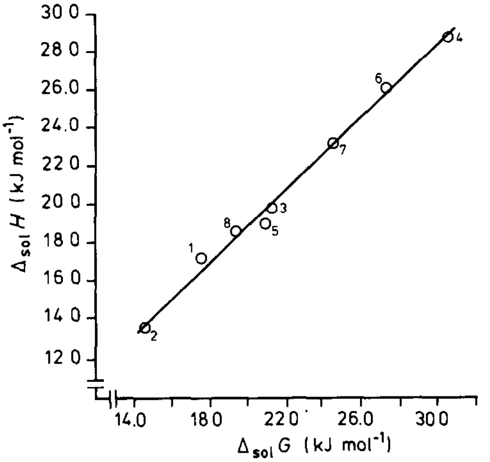


Fig. 1. Compensation analysis for solubility data at pK_u; numbers refer to powders as indicated in Table 1.

pensation. The isosteric data produced a linear relationship with a correlation coefficient of 0.999 and a compensation temperature (obtained from the gradient) of 297.5 K, and for the calorimetric data, the correlation was 0.999 and the compensation temperature was 299.3 K (Figs. 3 and 4). The compensation temperatures are in line with an equilibrium of thermodynamic functions occurring at the temperature of the experiment (298 K).

The ordering of the powders on the compensation plot produced from the calorimetric wetting data was in line with the rank order of wettability.

The values of the thermodynamic parameters of solution, whilst indicating the existence of a structure–activity relationship, revealed an unexpected ordering on the compensation plot, with the compounds not being arranged

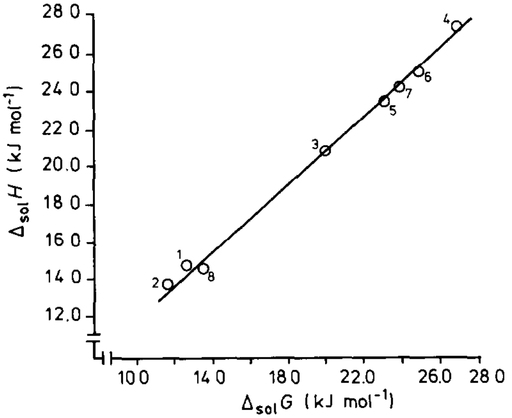


Fig. 2. Compensation analysis for solubility data at pK_a; numbers refer to powders as indicated in Table 1.

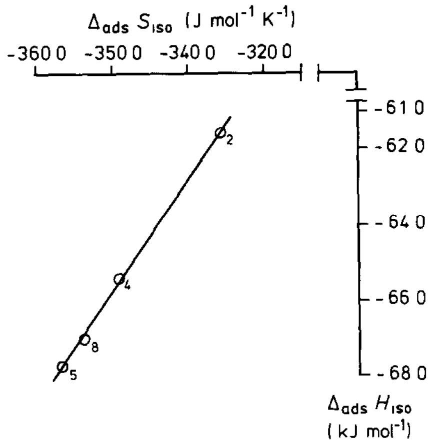


Fig. 3. Compensation analysis for the isosteric adsorption data; numbers refer to powders as indicated in Table 1.

in order of solubility. The ranking of the thermodynamic parameters of solution for the pK_u data was: phenobarbitone, butabarbitone, vinbarbitone, probarbitone, pentobarbitone, amylobarbitone, barbitone and butobarbitone. A similar trend was observed with the pK_a data. The complicated nature of the substituents makes it difficult to comment on this ordering of the compounds. There is clearly a need to undertake investigations of structure–activity relationships for homologous series of powders. It is possible that such experiments will yield compensation plots with a similar scatter of structures as that observed in this paper. However, with logical variations in chemical structure an explanation of this phenomenon may be possible.

The data described here suggest that, despite the existence of a structure–activity relationship for both wettability and solubility, the struc-

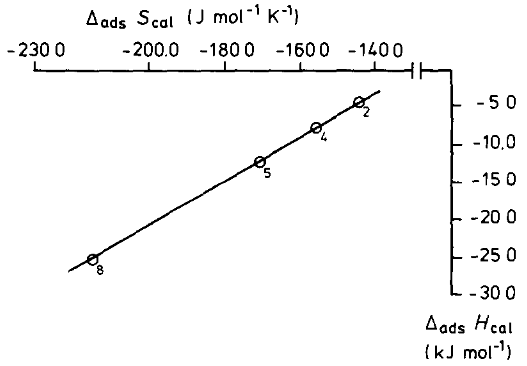


Fig. 4. Compensation analysis for the calorimetric adsorption data; numbers refer to powders as indicated in Table 1.

tural features required for a high degree of wettability are not necessarily related to those needed for high solubility in the wetting solvent. This fact is demonstrated by the results for phenobarbitone; this powder has a wettability intermediate between butobarbitone and pentobarbitone (four- and five-carbon chain substituents), but a solubility lower than both of these powders.

CONCLUSION

The idea of a structure–activity link for solubility has been established in part for many years. It is usually assumed that the aqueous solubility will decrease in a linear manner as a function of increased chain length. There is not always a simple linear relationship between chain length and solubility [1] and even when a linear response might be expected, the thermodynamics of solution reveal the process to be more complicated. There is no obvious explanation for the alignment of the compounds in the compensation plots reported here.

The solution process is complicated further as wetting also exhibits a structure–activity relationship. This initial (potentially rate-limiting) step in the solution process is too often ignored. Poor wetting may on occasions prevent the solution process occurring. It appears from the data presented here that the structural requirements for good wetting may not be those required for high solubility.

This paper serves to encourage workers to consider the structural influences on these physical properties and to encourage an interpretation of data leading to an understanding of the inter-relationships between wettability and solubility.

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