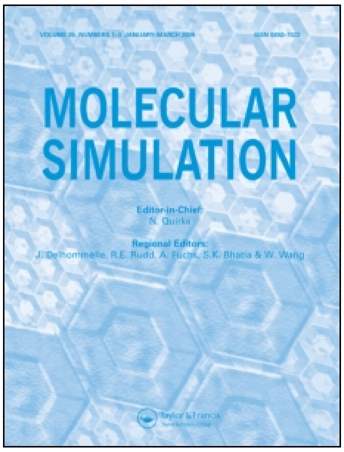

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Wetting of paracetamol surfaces studied by DMol^3-COSMO calculations

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Wetting of paracetamol surfaces studied by DMol^3-COSMO calculations

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Unrelaxed surface models of several relevant faces of the two polymorphic forms of paracetamol were studied by DMol^3-conductor-like screening model (COSMO) calculations. This is a computationally expedient first step towards a more complete study of wettability. Our calculated wetting energies for the different faces show a trend consistent with recent contact angle measurements for paracetamol and water. The orthorhombic (0 0 1) and the monoclinic (0 1 0) surfaces are the most stable ones in the dry state as well as in the wet state. The COSMO wetting energy for these two surfaces agrees very well with the values deduced from experiment. The calculated COSMO wetting energies for the other, more polar, surfaces are higher and get overestimated by the model.

Keywords: paracetamol; wetting; density functional theory; DMol^3-COSMO calculations

1. Introduction

The energetics and wetting properties of solid state materials are of great importance in the performance of pharmaceutical and chemical materials. A detailed knowledge of the surface chemical behaviour will assist in predicting surface properties such as solubility, adhesion, surfactant adsorption and many others.

Paracetamol is a compound with significant usage in the pharmaceutical industry. It is already known that the paracetamol crystal exhibits polymorphism. Three polymorphs of paracetamol have been reported in [1]: a thermodymanically stable monoclinic form I [2]; a metastable orthorhombic form II [3] and a very unstable form III. The monoclinic form I is the form used commercially, due to its thermodynamic stability at room temperature. In the current work, we investigate both forms I and II, in order to underline the difference in their chemical behaviour, and to point out that it is not possible to gain understanding about one form based upon the knowledge of another form.

Duncan-Hewitt and Nisman examined the wettability of paracetamol using several experimental techniques such as Washburn capillary rise method, sedimentation volume methods and the sessile drop determinations on compacts, films and single crystals [4]. It was concluded that these powder characterisation techniques have difficulties concerning sample preparation, data interpretation and methodology imprecision.

The semiempirical methods have been applied to evaluate surface free energy components of solid materials and polymer surfaces [5–10]. Owens and Wendt [6] developed a method for measuring the surface energy of solids and for resolving the surface energy into contributions from dispersion and dipole-hydrogen bonding forces. By measuring a contact angle of two different liquids against a solid, the components of surface free energy due to hydrogen bonding (γ^h) and dispersive forces (γ^d) can be estimated (the sum of these components should yield an approximation of the total solid surface energy). On the basis of this model, the surface energy could be predicted for other solvents with known γ^h and γ^d. Theoretical considerations for determination of surface energies and semiempirical methods are reviewed in [11].

Recent years have shown significant progress in the use of computation-based approaches for predicting surface energies and wettability. Continuum solvation models, in particular the conductor-like screening model (COSMO), are well-established methods to incorporate solvation effects into quantum chemical calculations. COSMO takes into account the detailed atomic structure of the interface interacting with the dielectric liquid.

In this work, the DMol^3-COSMO method [12,13] is applied with periodic boundary conditions. An extension to a wide class of liquids could be made by semiempirical 'real solvent' parametrisation as it is done routinely for solvent modelling [14]. This surface COSMO approach yields first principle prediction for the solid–liquid interfacial energy of a specific surface with an idealised high dielectric liquid.

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2. Method

The calculations reported in this work are performed by the all electron density functional theory (DFT) DMol^3 code [15,16]. Double numerical polarised (DNP) basis set which includes all occupied atomic orbitals plus a second set of valence orbitals plus polarised d-valence orbitals are employed. Atom element dependent cut off radii with medium size of 8.0 Å is applied. Perdew–Burke–Ernzerhof (PBE) [17] exchange-correlation potential is used. DMol^3 PBE calculations have been demonstrated to give a very successful account of reaction enthalpies of molecules in the gas phase [18]. A sufficient level of convergence for the COSMO solvent accessible surface (SAS) is reached using a 110 point scheme [19] for all atoms except hydrogen, where the 50 points scheme is used.

The lattice parameters that we used for the bulk geometry optimisation of the crystal structures are those reported by Haisa et al. [2,3]. The optimised bulk crystal structures are used for cleaving crystal surfaces, characterised by their Miller indexes. Crystal surfaces are kept fixed in the calculations and no relaxation of the surface structures is considered. The unrelaxed surface slab is constructed via a bulk primitive cell containing sides with the desired Miller index for the surface. Molecules are assigned entirely to the cell where the molecular centre of mass resides. The slab model here is one or two layers of such primitive cells. The choice of origin normal to the surface plane leaves a free parameter for constructing possibly different surfaces with the same index. The presence of an inversion symmetry element in both orthorhombic and monoclinic paracetamol leaves automatically symmetry equivalent faces on both sides when the slabs are comprised of an integer number of primitive cell layers.

Our present minimalistic slab models contain 80 atoms/cell, respectively, 160 atoms/cell in the case of the (201) surface and the orthorhombic form. In some cases, the back surface and the front surface of the slab derive from the same molecules. As the molecules are stiff compared to intermolecular bonding interactions, geometry optimisation should mainly adjust the relative geometry of molecular constituents. The authors feel that for thin slab models, as for the present ones, a geometry optimisation does not improve the realism of the solid–liquid interface. The molecules are placed according to the bulk crystal, but there are no bulk substrate constraining the position of surface molecules in the present thin slab models. Adsorbed molecules and hydrogen bonds to the surface can be studied with the present approach by adding such extra molecules explicitly, but this has not been tried yet. The present models turn out to contain the smaller number of atoms than a cluster construct for the surface, where additional molecules must be added to surround the surface cell of interest. Not surprisingly, the present calculations are not only more pleasing, but also faster than the cluster model for the corresponding surface.

Wetting of the surface are simulated by means of the COSMO method. Detailed methodology using the COSMO approach is given in a previous publication [12], but we briefly overview the SAS and the calculation of the solvation energy.

The DMol^3 is a method [15,16] for DFT calculations of molecular clusters in the gas phase. It is generalised [13] to model a solvent environment of a molecule via the COSMO [20]. This method involves the construction of a SAS and the solution of electrostatics. The SAS is defined via element-dependent radii, with values typically about 17% larger than the van der Waals radii. The SAS is a model of a surface where the induced charges are located. The detailed construction is discussed in a previous publication [12]. A new SAS grid construction [12] is tested, where the grid points and weights are a continuous function of all atomic geometries. The calculated solvation energy is also continuous by consequence, which is useful for all calculations that involve geometry changes of the atomic framework. The basic COSMO approach assumes that the screening takes place exactly on that surface and therefore, the name COSMO. The distribution of the screening charges contains information about the hydrophilicity of the surface (models can be generalised to take into account the different nature of the solvents). This information can, in principle, be used for improved semiempirical analysis like the COSMO-RS method [14].

The total solvation energy at the COSMO level is $E_{\mathrm{solv}} = E_{\mathrm{t}}(q) - E_{\mathrm{t}}(q = 0) + E_{\mathrm{diel}}$, where E_{t} is the total energy in the presence/absence of COSMO screening, q is the vector of the screening charges on the surface of the cavity and E_{diel} is the dielectric energy.

3. Results

3.1. *Surface energy*

The surface energy is the energy gain by wetting the surface. At the most basic level, static wetting is described by Young's law: $\gamma_{\mathrm{SL}} - \gamma_{\mathrm{SV}} + \gamma\cos(\theta) = 0$, where γ_{SV} is the surface energy of the solid against the gas phase and γ_{SL} against the liquid. γ is the surface tension of the liquid. At the COSMO level $\Delta\gamma = \gamma_{\mathrm{SL}} - \gamma_{\mathrm{SV}} = E_{\mathrm{solv}}/A_c$, the 'solvation energy' per planar surface area A_{c}. In a slab model A_{c} usually refers to the combined area from both sides of the slab. On the experimental side, contact angle measurements are an important tool to study liquid–solid interfacial energies. With Young's law one has $\Delta\gamma = -\gamma\cos(\theta)$. To convert the experimental contact angles from Ref. [21] to $\Delta\gamma$, the experimentally well-known surface tension of water $\gamma = 72.8$ mN/m is used.

Table 1. Wetting energies (mN/m) for paracetamol form I (molecules optimised in bulk structure).

Surface	Experiment [23,24]	Haisa et al. [2,3]	Cambridge database [22]	A_c
(2 0 1)	57.3	107.5	100.2	232.70
(0 0 1)	70.0	113.7	93.6	107.25
(0 1 1)	63.2	82.0	81.3	134.80
(1 1 0)	46.0	67.3	98.2	107.25
(0 1 0)	27.6	29.5	29.3	81.65

A_c is the surface area in (Å^2).

3.2. *Paracetamol form I*

The crystal structure parameters reported by Haisa et al. [2] are: $a = 12.93, b = 9.40, c = 7.10$ and $\beta = 115.9$ (*P21/a* group), while Cambridge database [22] gives values of $a = 7.0941$, $b = 9.2322$, $c = 11.6196$ and $\beta = 97.821$ (*P21/a* group, $a–c$ interchanged vs. the crystal structure resolved by Haisa et al. [2]). We report calculations for both crystal structures but, the discussion of the results is based on the crystal structures proposed by Haisa et al. [2]. Facet (0 1 0) exposes the hydrophobic methyl groups together with the amine and carbonyl ones. At the (0 1 0) surface, the lack of polar groups determines the low attachment energy of this facet. Facets (2 0 1), (0 0 1) and (0 1 1) have similar functional group contributions and the differences are due to the different densities of the methyl, amine and carbonyl groups and their orientation at the surface. These differences give rise to different interactions. In line with the COSMO calculations presented here, surface energies, calculated from the measured advancing contact angle [23,24] indicated relatively high energy contributions on facets (2 0 1), (0 0 1) and (0 1 1). The surface energy on facet (1 1 0) was lower. The surface energy on the facet (0 1 0) was even lower and confirmed that the surface is hydrophobic and possesses minimal potential for hydrogen bond interactions. Wetting energies and surface areas for paracetamol form I (molecules optimised in bulk structures) are given in Table 1.

3.3. *Paracetamol form II*

The crystal structure parameters reported by Haisa et al. [3] are: $a = 11.805$, $b = 17.164$ and $c = 7.393$ (*Pcab* group), while Cambridge database [22] proposes values of $a = 17.1657$, $b = 11.7773$ and $c = 7.212$ (*Pbca* group, $a–b$ interchanged vs. the crystal structure resolved by Haisa et al. [3]).

For the form II, the trend in the surface energy is the opposite of that of form I, i.e. the hydrophobic (0 0 1) facet with low surface energy and hydrophilic (1 1 0) and (0 1 0) facets with similar energy. While the COSMO calculations and the experiments agree well on the surface energy for the (0 0 1) surface, there is almost a factor of two disagreement for the (0 1 0) and (1 1 0) facets. The maximum value of the calculated wetting energy, based on the advancing contact angle measurements, is 72.8 mJ/m^2 ($\gamma \cos(\theta)$). For surfaces (1 1 0) and (0 1 0) this maximum wetting energy value is approached. On the contrary, the COSMO method is not limited to maximum wetting energy value of 72.8 mJ/m^2 and could get any positive number. Quantitatively, the two methods agree in distinguishing the hydrophilic (1 1 0) and (0 1 0) surfaces from the hydrophobic (0 0 1) surface of the orthorhombic polymorphic form of the paracetamol crystal. Wetting energies and surface areas for paracetamol form II (molecules optimised in bulk structures) are given in Table 2.

4. Discussion

Our calculations show that the dependence of the wetting behaviour of the polymorphic crystalline paracetamol forms I and II on their Miller indices is not obvious. For forms I and II, the facets (0 0 1) and (2 0 1) are the most hydrophilic, respectively (Table 1), whereas the facet (0 0 1) is the most hydrophobic (Table 2). These results show, that the hydrophilicity trends are opposite for forms I and II. Similar conclusions are drawn from the experimental studies of Heng et al. [23,24]. From the

Table 2. Wetting energies (mN/m) for paracetamol form II (molecules optimised in bulk structure).

Surface	Experiment [23,24]	Haisa et al. [2,3]	Cambridge database [22]	A_c
(0 0 1)	31.3	30.1	22.6	207.15
(1 1 0)	69.8	126	116.8	150.15
(0 1 0)	69.3	111	124.5	84.95

A_c is the surface area in (Å^2).

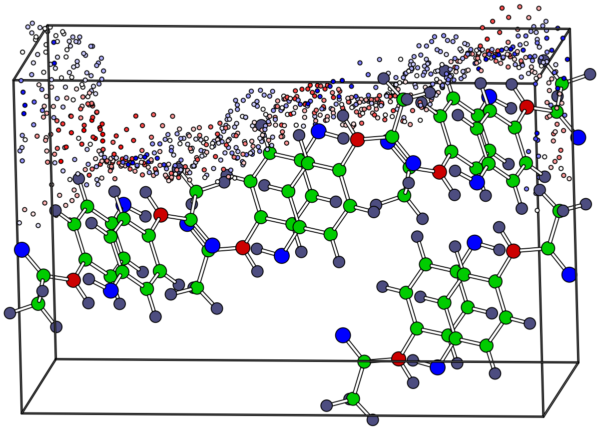

Figure 1. COSMO charges for the hydrohylated monoclinic (2 0 1) paracetamol surface, green balls are the carbon atoms, red, nitrogen atoms, blue, oxygen atoms and dark blue, hydrogen atoms. Colour code for COSMO charges, blue, $-2\,\mathrm{e/nm^2}$, red $+2\,\mathrm{e/nm^2}$ and white zero. Upper half of the COSMO surface is shown, face of cell indicates atomic surface plane.

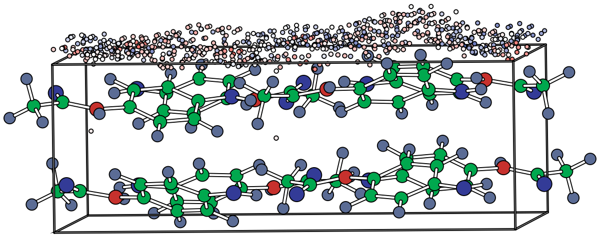

Figure 2. COSMO charges for the hydrohylated orthorhombic (0 0 1) paracetamol surface, green balls are the carbon atoms, red, nitrogen atoms; blue, oxygen atoms and dark blue, hydrogen atoms. Colour code for COSMO charges, blue $-2\,\mathrm{e/nm^2}$, red $+2\,\mathrm{e/nm^2}$ and white zero. Upper half of the COSMO surface is shown, face of cell indicates atomic surface plane.

measurements of advancing contact angles, the orders of hydrophilicity for the specific facets of forms I and II are

$$(0\,0\,1) > (0\,1\,1) > (2\,0\,1) > (1\,1\,0) > (0\,1\,0)\ \text{(form I)},$$
$$(0\,1\,0) \approx (1\,1\,0) > (0\,0\,1)\ \text{(form II)},$$

while COSMO orders them in the following sequence (based on the crystal structures proposed by Haisa et al. [2,3])

$$(0\,0\,1) > (2\,0\,1) > (0\,1\,1) > (1\,1\,0) > (0\,1\,0)\ \text{(form I)},$$
$$(1\,1\,0) > (0\,1\,0) > (0\,0\,1)\ \text{(form II)}.$$

As mentioned before, the calculations are done with optimised bulk coordinates. The calculation of the surface structures, however, does not include relaxation and reconstruction. A possible relaxation/reconstruction of the surface might lower the surface energy. To be able to account for these, one has to consider bigger surfaces, which in turns, makes the calculations more expensive. The SAS for the (2 0 1) surface of the monoclinic paracetamol (form I), shown to be highly hydrophilic, and for the most hydrophobic (0 0 1) surface of the orthorhombic paracetamol (form II) are shown in Figures 1 and 2, respectively. The SAS is strongly corrugated for the (2 0 1) surface of the monoclinic paracetamol (form I) and not so much for the (0 0 1) surface of the orthorhombic paracetamol (form II).

Figure 3 gives a comparison of the COSMO results and H_2O experimental wetting energies from the work of Heng et al. [23,24], using the structures proposed by Haisa et al. [2,3] and Cambridge database structures [22] with reference numbers 135451/135452 and interpreting Cambridge results in Haisa crystal setting. A similar (relatively good) correlation is found between the theoretical results calculated with the both structures (proposed by Haisa et al. [2,3] and Cambridge database structures [22]) and the experimental results based on the measurements of the advancing contact angle [23,24].

The orthorhombic (0 0 1) and the monoclinic (0 1 0) surfaces are the most stable ones in the dry and wet states. The COSMO approach reproduces very well the experimental values of the wetting energies for these two surfaces. The calculated COSMO wetting energies for the other, more polar, surfaces are higher and get overestimated by the model. It is difficult to estimate how the wetting energy of the more polar and naturally less stable surfaces would be reduced to approach experimental values more closely. One may speculate that, since these surfaces are not very stable, significant surface relaxation

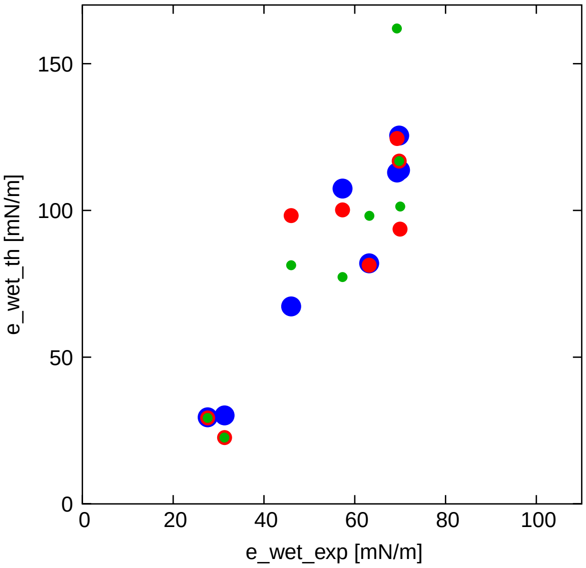

Figure 3. Comparison of the COSMO results and H_2O experimental [23,24]: blue, using crystal structures proposed by Haisa et al. [2,3]; red, using Cambridge database structures [22] with reference numbers 135451/135452 and green interpreting Cambridge results in Haisa crystal setting.

and reconstruction, perhaps several molecular layers deep, might take place. Geometry optimisation of sufficiently thick slab models ought to show this effect if it is real.

The COSMO model involves a fictitious conductor with no limitation of the screening charge density. Even when scaled to the proper dielectric constant, this remains true. However, a real solvent has a fairly well defined set of available surface charge densities as evidenced in the so called 'sigma profile' [14]. The postprocessing of COSMO results as the present ones with the real solvent model are expected to make these wetting energies more realistic.

5. Summary and conclusion

This study presents a hydrophilicity ranking for several facets of paracetamol forms I and II, which is based on the calculated wetting behaviour by means of the COSMO approach. The local surface chemistry for the different facets are defined by the methyl, amine and carbonyl groups present on the surface. Surfaces with the same Miller indices for forms I and II paracetamol shows entirely opposite trends in their surface chemical behaviour. The most hydrophilic surface for form I, (0 0 1), is the most hydrophobic one for form II, while one of the most hydrophilic surfaces for form II, (0 1 0), is the most hydrophobic for form I. Therefore, knowledge of wettability for one of the polymorphic forms of paracetamol cannot be directly applicable on other polymorphic form.

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