



# Heterogeneous nucleation of polymorphs on polymer surfaces: polymer–molecule interactions using a Coulomb and van der Waals model

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## Abstract

The nucleation processes of acetaminophen on poly(methyl methacrylate) and poly(vinyl acetate) have been investigated and the mechanisms of the processes are studied. This is achieved by a combination of theoretical models and computational investigations within the framework of a modified QM/MM method; a Coulomb–van der Waals model. We have combined quantum mechanical computations and electrostatic models at the atomistic level for investigating the stability of different orientations of acetaminophen on the polymer surfaces. Based on the Coulomb–van der Waals model, we have determined the most stable orientation to be a flat orientation, and the strongest interaction is seen between poly(vinyl acetate) and the molecule in a flat orientation in vacuum.

**Keywords** Nucleation processes · Acetaminophen on polymers · Modified QM/MM method · Molecule polymer interface

## Introduction

Different definitions of polymorphism have been proposed over the years. McCrone's definition of polymorphism captures the concept very well: "A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state" [1]. Another somewhat weaker definition is given by Buerger, who characterizes polymorphs as crystal forms with different properties [2]. Though McCrone's definition is more scientifically correct, Buerger's definition states the impact of polymorphism—two polymorphic forms rarely have identical physical properties.

Polymorphism has received an increased amount of attention from the pharmaceutical industry due to

intellectual property and bioavailability. A patent generally applies to a specific polymorphic form, and the recognition of a previously unidentified polymorphic form can potentially undermine the patent [3]. Ritonavir is an example of how critical a polymorphic change can be. This antiviral drug was lanced against AIDS in 1996 as capsules. During the development, only one crystal form was identified, and this form was produced until the middle of 1998. In mid-1998, a new polymorph of ritonavir was identified from the production with crucially different physical properties. Within weeks, the second, more stable, polymorph appeared in the pure drug and capsules. The drug was prepared from a hydroalcoholic solution, in a concentration where the first polymorph was dissolvable while the second form was 400% supersaturated [4]. Additionally, the drug could no longer be stored in a solution for oral intake because of the risk of crystallization. In the end, the drug was reformulated in refrigerated gelcaps, which are still available. The story of ritonavir demonstrates the importance of controlling the crystallization process and knowing the thermodynamic most stable polymorph.

Even though polymorphism has received an increased amount of attention, the phenomenon is far from a recent discovery. Polymorphism was reported for the first time in 1832 by Wöhler and Liebig [5], who observed phase transitions between two different forms of benzamide.

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Since 1832, the number of compounds known to be polymorphic has increased dramatically; in 1990 only 4,618 polymorphic compounds were known, this number was increased to 17,232 in 2011 [6]. It is impossible to say how many unidentified polymorphic forms a compound has, but McCrone has an excellent comment regarding this: “the number of forms known for a given compound is proportional to the time spent in research on that compound” [7]. But this is not always the case; ibuprofen is produced in millions of kilograms per year and still only one crystal form is known [3]. On the other hand, during the development of DMP 543, a drug against Alzheimer’s disease, 17 polymorphic forms were discovered [8]. Estimates of how many organic compounds are polymorphic range between 50% [9] and 80% [10].

Polymorphism is due to different molecular packing in the crystals. The different packing motifs give rise to different internal energies, since the potential energy relies on the bonds; inter- as well as intramolecular. The relative stability of two polymorphs is determined by the free energy; the form with the lowest free energy is the most stable form, while the other form is metastable. If one polymorphic form at all temperatures is the most stable form, they are said to be monotropically related. If, on the other hand, the relative stability of the polymorphic forms changes at any temperature, they are enantiotropically related. Though, not having the lowest free energy, metastable forms exist and have lifetimes ranging from minutes to years. If the energy barrier for creating the metastable form is lower than the barrier for crystallizing the stable, the metastable may very well crystallize first. Indeed Ostwald’s rule state that the first appearing polymorphic forms in a crystallization experiment is the least stable.

Acetaminophen, also known as paracetamol, is a widely used antipyretic and analgesic drug, and has therefore been subjected to thorough investigations. Three polymorphic forms are known, where form III is metastable and only observed under special circumstances [11]. The monoclinic [12] (form I) and orthorhombic [13] (form II) forms are stable at ambient conditions, and the physical [14] and thermodynamical [15, 16] properties have been studied alongside with the structural composition. Form I is commercially available, although form II is compressed easily to tablets due to higher plasticity [17]. The thermodynamic relationships between the two forms have been subjected to some discussion. The transition enthalpy has been determined multiple times and the results are ambiguous; ranging from the transition  $II \rightarrow I$  being endothermic to exothermic. The transition enthalpy and temperature were first determined by Burger to be +0.4kJ/mol and 360 K, respectively [18]. Later, both have been redetermined several times, which have led to several different results, see Table 1. The transition enthalpy derived

by Sacchetti is based on the enthalpies of fusion obtained at 160 °C (form II) and 172 °C (form I). To compare the two values, one has to measure or derive them at the same temperature. By using Kirchhoff’s law, Eq. 1, and assuming a constant difference between the solid and liquid heat capacities in the temperature interval, we can derive a more correct transition enthalpy. [16]

$$\Delta H_{fus}(T_2) = \Delta H_{fus}(T_1) + \int_{T_1}^{T_2} \Delta_{fus} C_p dT \quad (1)$$

If the heat capacity is assumed to be 80J/(mol · K), the enthalpy of fusion of form I at the transition temperatures of form II is

$$\begin{aligned} \Delta H_{I,fus}(433K) &= 28.1\text{kJ/mol} \\ &+ \int_{445K}^{433K} 80 \cdot 10^{-3}\text{kJ}/(\text{mol} \cdot \text{K})dT \\ &= 28.1\text{kJ/mol} \\ &- 12\text{K} \cdot 80 \cdot 10^{-3}\text{kJ}/(\text{mol} \cdot \text{K}) \\ &= 27.1\text{kJ/mol} \end{aligned} \quad (2)$$

Since  $\Delta H_{II,fus}(433K)$  was measured to be 27.6 kJ/mol, the transition enthalpy,  $\Delta H_{II \rightarrow I}$  at 433 K, is -0.5 kJ/mol. By including a standard heat capacity, the enthalpy changes from -0.5 kJ/mol to +0.6 kJ/mol. The ambiguity of this example clearly shows the uncertainty of not only the measurement itself, but of the interpretation of the results as well. Though the enthalpy difference between form I and II is determined with some uncertainty, the thermodynamic relationship between the two polymorphs is believed to be monotropic, with form I being the thermodynamically most stable. That is, at all temperatures, form I is the thermodynamically stable form, while form II at all times is a metastable form only allowed due to kinetic factors.

The use of polymers as heteronuclei was first proposed by Matzger [21]. In the initial investigations, a polymer library, containing 84 polymers, was used in the form supplied by the manufacturer, i.e., beads and blocks. Acetaminophen and carbamazepine, known to have two polymorphic forms prior to this study, were investigated. Both known forms and two new of carbamazepine were obtained. Later, the importance of the polymer composition was investigated by using copolymers with different ratios of polymer and the crosslinker divinylbenzene [22]. Here, carbamazepine, sulfamethoxazole, and ROY were investigated and multiple, but not all known, polymorphic forms, were recovered. The conclusion of the experiments was that the polymers were able to induce different polymorphic forms. To rule out surface roughness, similar experiments were conducted but with the polymers spin coated on cover slides and the results were in line with the previously reported results. In addition, molecular dynamics (MD) simulations were conducted to explain the results

**Table 1**  $\Delta H_{(I \rightarrow I)}$ 

	$T_{tr}$ (observed)	$\Delta H_{I \rightarrow I}$	Sample source	Thermodynamic relationship
Burger [18]	360 K	+0.4 kJ/mol	From melt	presumed enantiotropic
Sacchetti [19] <sup>a</sup>	estimate: 153.15 K	−0.5 kJ/mol		Enantiotropic
Sacchetti [19] <sup>b</sup>	—	+0.6 kJ/mol	—	—
Espeau [16]	—	−0.51 kJ/mol	From melt	Monotropic
Boldyreva [15]	373 K	+0.54 kJ/mol	From aqueous solution	Monotropic
Perlovich [20]	—	−2.0 kJ/mol <sup>c</sup>	From melt	Monotropic

<sup>a</sup>This value is calculated from the melting enthalpies,  $\Delta_{I \rightarrow I}H$  and  $\Delta_{II \rightarrow I}$ , obtained at different temperatures. The heat capacity is thus neglected.

<sup>b</sup>See text. <sup>c</sup>Solution calorimetry

[23]. In the MD simulations, a reverse approach to the crystallization was taken: Instead of an acetaminophen molecule on a polymer surface, an oligomer of the polymer was modeled on different surfaces of the crystal. The polymers poly(methyl methacrylate) and poly(*n*-butyl methacrylate) have been studied with sum frequency generation (SFG) where it has been established that the surface mainly consists of the ester methyl group oriented along the surface [24].

We consider a modified QM/MM method for investigating the interactions between a polymer surface and a molecular system approaching the polymer surface. We have utilized a Coulomb and van der Waals method for investigating polymer–molecule interactions and we compare this method to a previously established dielectric medium model [25]. In the dielectric medium model, the solid surface is modeled by an isotropic dielectric constant. In this presentation, we focus on a chemical understanding of the surface–molecule interactions and this requires that the atoms in the polymer and the molecule are represented by an atomistic model having partial charges, and a Lennard–Jones potential to model the van der Waals interactions. The system is divided into two parts: a molecular and a polymer subsystem, and it is assumed that the internal energies of the subsystems are satisfactorily determined by the initial quantum mechanical calculations used to optimize the geometries of the molecules and the polymers and also determine the atomic charges. The Coulomb energy is the classical electrostatic interaction between two charged particles, while the van der Waals energy is the interaction from the non-permanent dipoles resulting from charge fluctuations. The electrostatic interaction considers the charge–charge interactions between the partial charges in the two subsystems. We focus on the flat conformations of acetaminophen when investigating the interactions between the molecular and polymer surface.

In the second section, we present the model that is used along with the parameters for the model. Furthermore, we show the different conformations of acetaminophen along

and how the molecule can approach the surface of the polymer. The polymer surface is given by a layer of ten monomers times ten monomers. We consider two different polymer surfaces: PMMA and PVA. The third section contains the results obtained for PMMA and the section is divided into two parts; one part concerns the polymer surface formed by the *cis* PMMA monomeric unit. In the other part of the third section, we consider the polymer surface formed by using the *trans* PMMA monomeric unit. In the fourth section, our focus is on the polymer surface containing PVA as a monomeric unit. We compare the obtained results in the fifth section and in the sixth section we discuss the results from the present model with results from other approaches. Finally, the seventh section contains a conclusion of the work.

## The modified QM/MM method and the parameters used

The general form of the van der Waals interaction energy is:

$$E_{vdW}(R^{AB}) = E_{repulsion}(R^{AB}) - \frac{C^{AB}}{(R^{AB})^6} \quad (3)$$

and we use the Lennard–Jones potential, which between atom A and B is:

$$E_{LJ}(R^{AB}) = \frac{C_1}{(R^{AB})^{12}} - \frac{C_2}{(R^{AB})^6} \quad (4)$$

and we rewrite this as

$$E_{LJ} = \sum_{s=1}^S \sum_{m=1}^M 4\epsilon_{sm} \left( \left( \frac{\sigma_{sm}}{R_{sm}} \right)^{12} - \left( \frac{\sigma_{sm}}{R_{sm}} \right)^6 \right) \quad (5)$$

The sums are of all the atoms in the molecular, *m*, and the solid, *s*, subsystems. The constant  $\sigma_{sm}$  and  $\epsilon_{sm}$  are the Lennard–Jones parameters, and have the units Å and eV. In Table 2 the Lennard–Jones parameters used to determine the interaction are listed [26]. The combined parameters

**Table 2** Lennard–Jones parameters [26]

Atom	$\sigma$ (Å)	$\epsilon$ (kcal/mol)	$\epsilon$ (eV)
C	3.80	0.08	0.0035
H (on C)	2.60	0.008	0.00035
O	3.60	0.15	0.0065
N	3.90	0.20	0.0087
H (on heteroatoms)	1.30	0.10	0.0043

used in Eq. 5 are determined as  $\sigma_{AB} = \sqrt{\sigma_A \cdot \sigma_B}$  and  $\epsilon_{AB} = \sqrt{\epsilon_A \cdot \epsilon_B}$ .

In addition to the Lennard–Jones energy, a Coulomb energy contribution between molecule and polymer is determined. The potential energy arising from the Coulomb interaction is:

$$E_{coulomb} = k_e \sum_{s=1}^S \sum_{m=1}^M \frac{q_s q_m}{|\vec{r}_m - \vec{r}_s|} \quad (6)$$

The partial charges on the atoms are determined by the CHelpG algorithm [27] in the Gaussian program [28]. We have used the DFT functional CAM-B3LYP [29] and the basis set aug-cc-pVTZ [30, 31], and the partial charges are presented in Table 3a and b. The charges are in atomic units while the distance is in Ångström. In Fig. 1, we present the labeling of the atoms in PVA and PMMA. We show in Fig. 2 the different conformations of acetaminophen and in Fig. 3 we show how a conformer is approaching the surface in six different orientations. The investigated orientations of the **ac** conformation are the same as those for **af** conformation and they are named in the same manner.

## Energy minimization

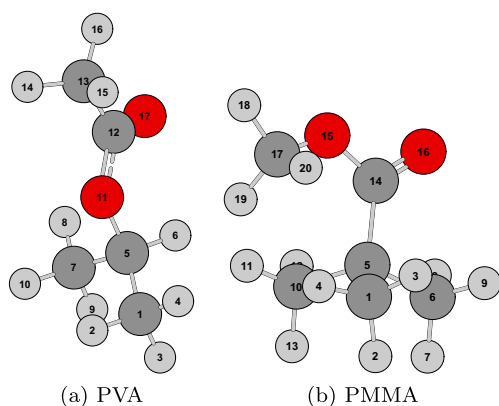
The surface is here defined as  $z = 0$ , and the polymer has atoms placed in the space  $z \leq 0$ . The distances in the energy diagrams is the lowest  $z$  component of the positions of the atoms in the molecule.

When the surface consists of distinct atoms and molecules, it is structured, thus the interaction energy depends on the rotation around the  $z$ -axis. The polymer surface is made up of monomeric units expanded to a ten monomer times ten monomer surface, and can be thought of as a two-dimensional periodic lattice. Since the monomeric units have different conformations, we end up having to consider several different polymer surfaces for each of the conformations of acetaminophen. The monomeric units are assigned a rectangle where the edges are determined as the longest spacing in the  $x$ - and  $y$ -directions. The lattice is constructed by placing the rectangles, including monomer, next to each other ten times. We assume a periodic arrangement of the polymer. This is of course wrong since polymers are amorphous materials. Though

**Table 3** Atomic charges of PMMA and PVA determined by CHelpG algorithm and CAM-B3LYP/aug-cc-pVTZ electronic structure method

Atom	<i>trans</i> -PMMA	<i>cis</i> -PMMA
(a) PMMA		
C(1)	−0.285057	−0.238389
H(2)	0.061641	0.068339
H(3)	0.059862	0.046189
H(4)	0.046468	0.037236
C(5)	0.506256	0.295718
C(6)	−0.398450	−0.341097
H(7)	0.082179	0.079321
H(8)	0.102980	0.076993
H(9)	0.082310	0.076994
C(10)	−0.393598	−0.238401
H(11)	0.096618	0.037237
H(12)	0.083798	0.046194
H(13)	0.086600	0.068345
C(14)	0.588133	0.691164
O(15)	−0.390168	−0.332459
O(16)	−0.538811	−0.560018
C(17)	0.109293	−0.074881
H(18)	0.060049	0.085104
H(19)	0.005642	0.085105
H(20)	0.034253	0.091305
(b) PVA		
Atom	PVA	
C(1)	−0.369242	
H(2)	0.088354	
H(3)	0.075611	
H(4)	0.100701	
C(5)	0.630073	
H(6)	−0.037355	
C(7)	−0.410242	
H(8)	0.098545	
H(9)	0.085545	
H(10)	0.112872	
O(11)	−0.556975	
C(12)	0.833610	
C(13)	−0.391814	
H(14)	0.115628	
H(15)	0.114717	
H(16)	0.103155	
O(17)	−0.593183	

some molecular characteristics of the surface are known from experiments [32, 33], six or seven orientations of the monomer were used. By using different orientations and combining the results, a more complete picture of the interaction energy curves is obtained. We do not consider the effects of the edges, since the molecule will not be



**Fig. 1** The labeling of the atoms

located at the edges at the experimental set-up and we consider the constructed surface along with the grid spacing to be sufficient for describing the interactions between the molecule and the polymer surface.

Because of the structured surface, the molecule in one of the six orientations has to be rotated and translated in the polymeric “unit cell”. In Fig. 4, the translational vectors and rotational direction of the molecule are shown. The interaction energy between molecule and polymer is determined at a number of points on the translational vectors and the same number of rotations. The orientation and position having the lowest energy is considered to be the minimum, and the geometry is denoted by the translation in the  $x$  and  $y$  direction,  $l_x$  and  $l_y$ , and the rotational angle,  $\nu$ . We ensure that the obtained energy grid is sufficiently accurate by using small grid spacings. The number of points in the two translational directions are the same, and only two numbers are needed to identify the number of points used in the energy minimizations. This procedure is not referred to as a geometry optimization, since the internal geometries of the two subsystems are constant. We keep the intramolecular structures fixed as in traditional molecular dynamics simulations.

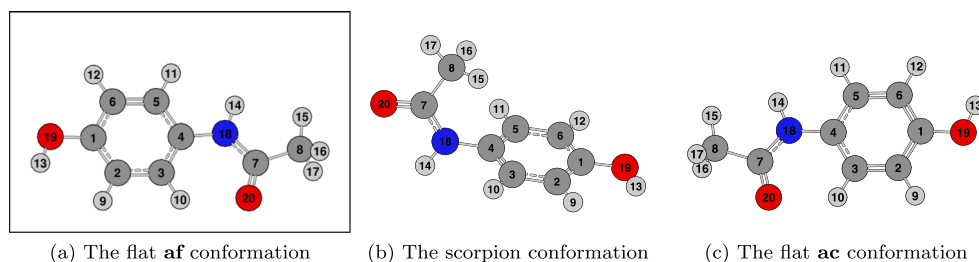
In Fig. 5, different grid spacings are used on the **ac5** molecular orientation and *cis*-PMMA polymer in orientation 2. The optimizations using two and six points are in separate coordinate systems since they coincide with the energy curve using ten points. The reason is that the

lowest energy in all three searches is obtained at the same position and geometry (either  $(0,0,0)$ ,  $(1/2l_x, 1/2l_y, 1/2\pi)$ , or a combination). The randomness of the algorithm is evident when comparing the four-point to the ten-point energy minimization; though searching significantly less points, 64 independent energy calculations compared to 1000, the four-point search ends up finding the lowest energy. The finest spaced grids,  $12 \times 12$  and  $30 \times 30$ , seem in this case to perform equally well, though on different time scales. In the  $12 \times 12$  optimization (really  $12 \times 12 \times 12$ , since the  $l_x$  and  $l_y$  vectors are divided by the same number of points) 1728 independent energy calculations are carried out compared to 27,000 in  $30 \times 30$  optimization. The lowest energy of a single molecular conformation in the  $12 \times 12$  point grid is derived in 10 min, while the time is increased by a factor of 15.625 for the  $30 \times 30$  grid, which is approximately 2.5 h. For that reason, the  $12 \times 12$  grid is used for the energy minimization.

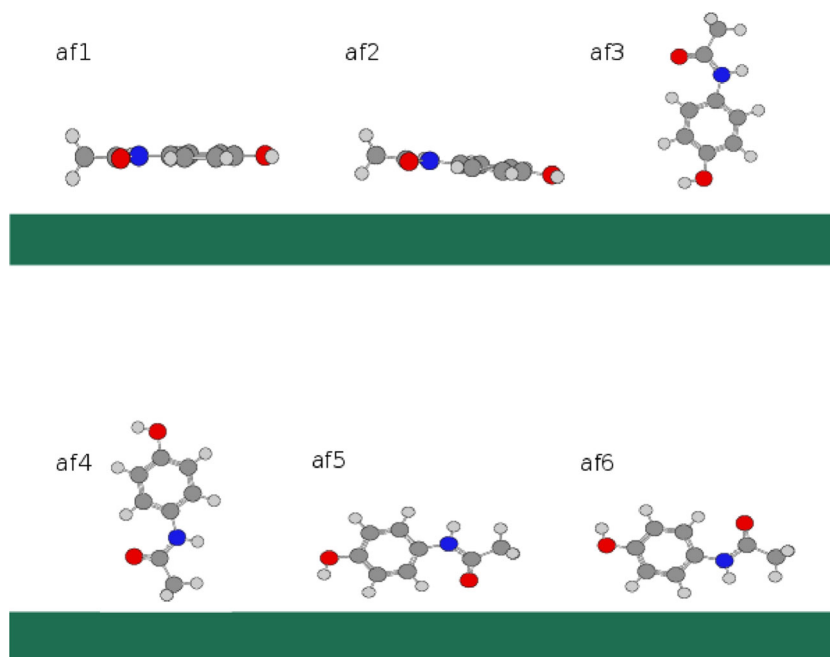
## PMMA

The PMMA monomer has two distinct conformations; the methyl group can point in the same direction as the carboxy-oxygen, denoted *cis*, or in the opposite direction, denoted *trans*. From experiments [32], a PMMA surface is known to be dominated by the methyl side chain in the *cis* conformation (Fig. 7g). Since the surface of a polymer is far from crystalline, other orientations are taken into consideration. Further, the *trans* conformation of the monomer is taken into consideration as well. Since the side chain is subjected to external forces, it may in some cases bend away from the surface. The orientations of the *cis*- and *trans*-PMMA monomers are shown in Figs. 6 and 7. It is highly unlikely that the surface only consists of backbone, due to geometrical and hydrophobic-hydrophilic constrains. Indeed, from sum-frequency generation vibrational spectroscopy, the surface is known to be dominated by the side chain [32]. Smaller domains with fully or partially exposed backbone may exist, and the monomeric orientations with the backbone as the surface is therefore also investigated. By combining the results from the individual orientations, a

**Fig. 2** The conformations of acetaminophen with labeled atoms



**Fig. 3** The orientations of the flat conformations

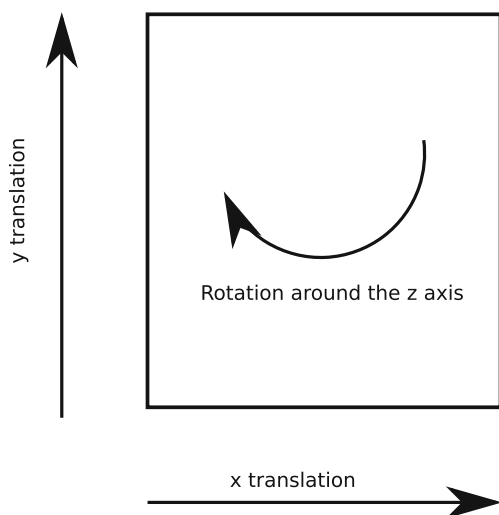


more detailed insight into the polymer–molecule interaction will be obtained.

**cis-PMMA** In Figs. 8 and 9, the energies of a molecule in **af** and **ac** conformations approaching the *cis*-PMMA surface are shown. In all orientations of the PMMA monomer, the flat orientations of both conformations, numbers **1** and **2**, have the lowest energy, followed by the sideways orientations, numbers **5** and **6**, and with the vertical orientations, numbers **3** and **4**, having the highest energy. The flat orientations have the lowest energy at 1 to 2.5 Å, where, due to being slightly tilted, orientation 2 is

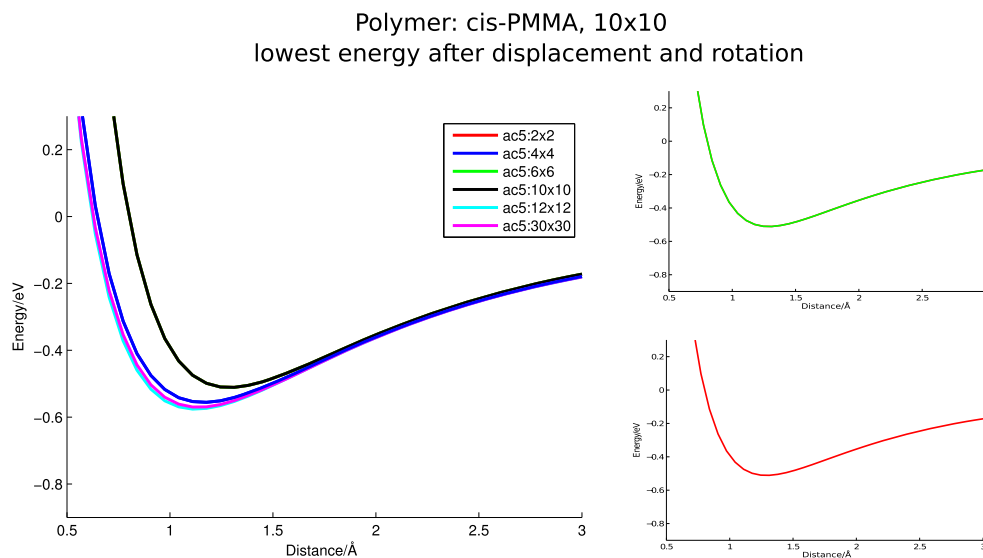
approximately 0.5 Å further away from the surface than orientation 1. The sideways and vertical orientations are approximately 0.5 Å closer to the surface than orientation 1, when the lowest energy is reached. The flat orientations cover a greater area on the polymer surface than the other conformations. The possibility of the polymer side chain blocking the molecule from approaching the surface at some point is greater for the flat than for the other orientations (Fig. 10). The vertical and sideways orientations of both conformations have the energy minima at the same distance from the surface. One would expect the vertical orientations to have the energy minimum closer to the surface than the sideways, since these orientations cover a smaller area, and it is more probable that a small area is free from the polymer side chains. The periodic model of the surface has the disadvantage of creating unreal long striations, which fit the sideways orientations. In Fig. 11, the voids of *cis*-PMMA1 are shown with a molecule of **ac3** conformation and orientation on the surface. Assuming that such voids do exist on the surface, the energy of the sideways orientation is 0.2–0.4 eV lower than the energy of the vertical orientations. The energy of the flat orientations is lowered by 0.1 to 0.25 eV compared to the sideways orientations.

Overall, the molecular conformations behave very similar: the flat orientations interact strongest with the surface regardless of the monomer orientation, followed by the sideways orientations and the vertical interacts least with the polymer. The flat orientation has the advantage of all the atoms in the molecule being close to the surface, and the energy from the interacting charges and Lennard–Jones potential is increased. The repulsion arising from two

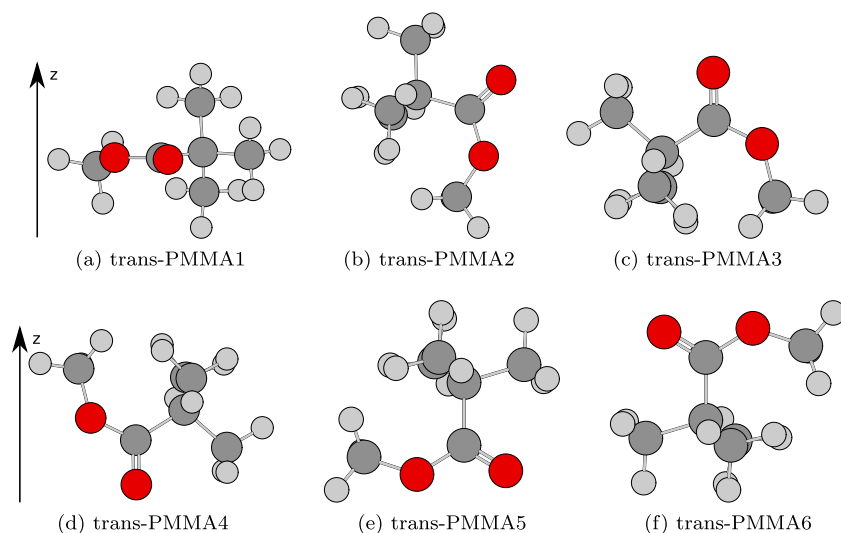


**Fig. 4** The translational vectors and the rotation of the molecule in the polymeric “unit cell”

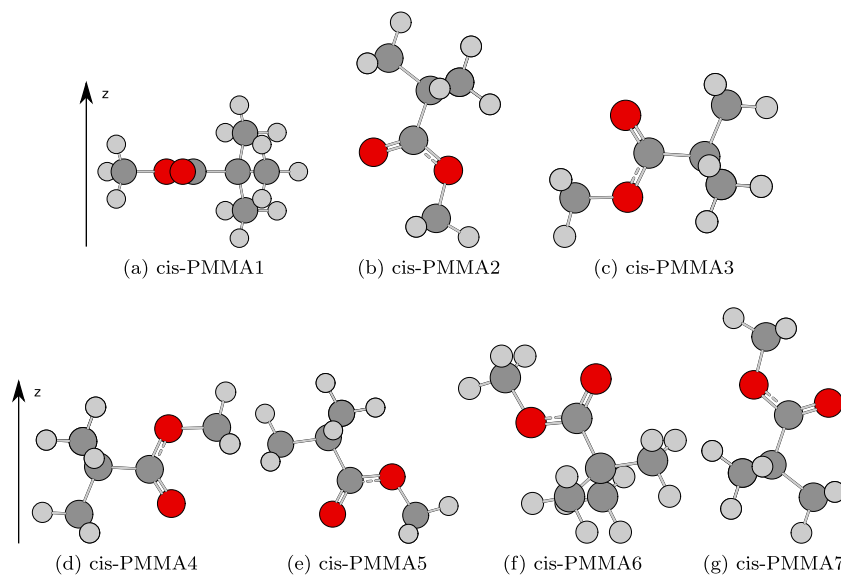
**Fig. 5** Calculation of the energy curves for different number of grid point when energy optimizing of the interaction between the **ac5** molecular orientation, and the *cis*-PMMA in orientation 2

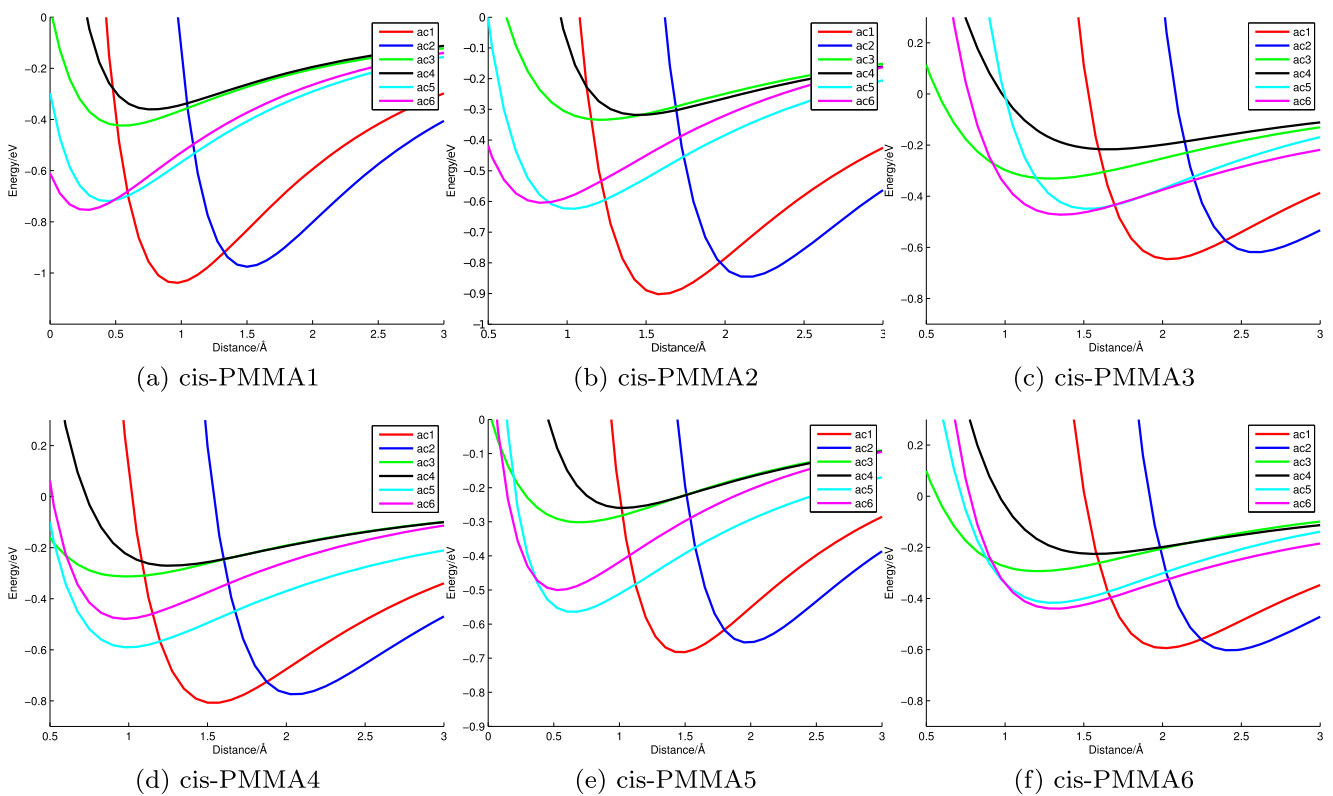


**Fig. 6** *trans*-PMMA monomeric unit orientation

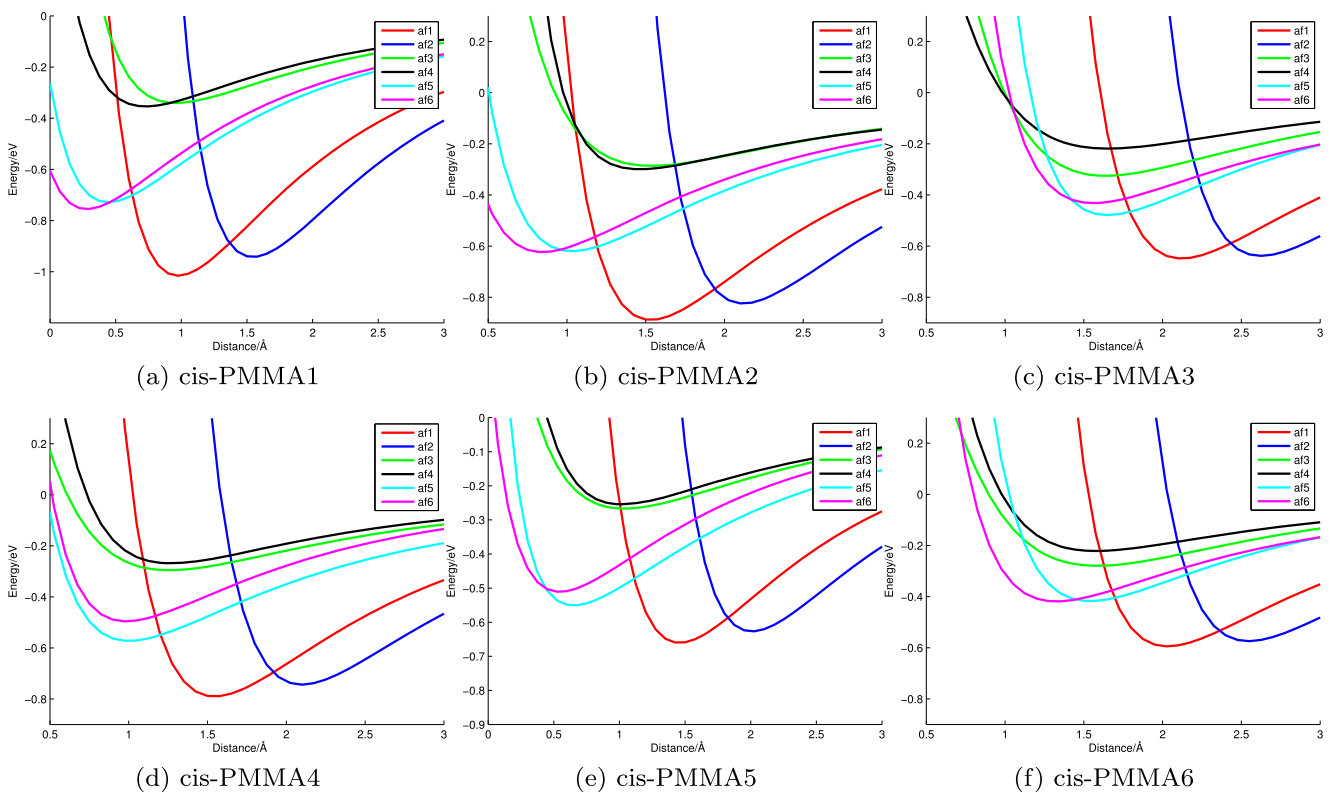


**Fig. 7** *cis*-PMMA monomeric unit orientation



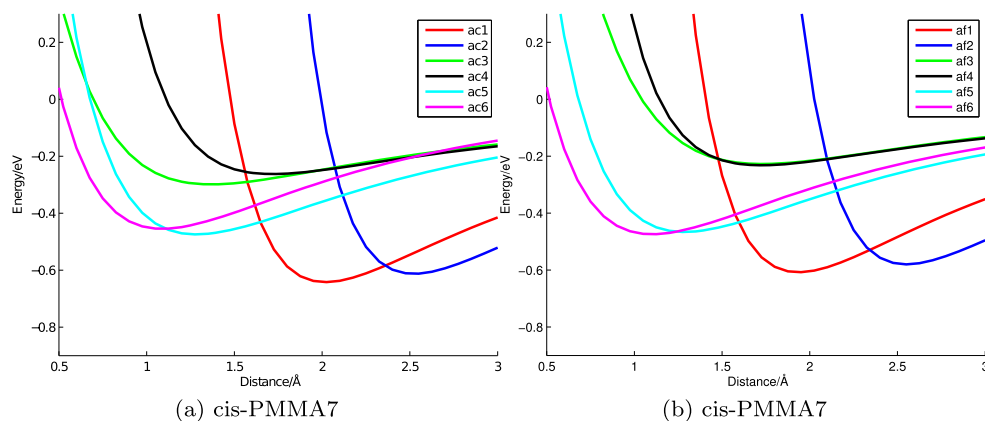


**Fig. 8** *cis*-PMMA and the ac conformation



**Fig. 9** *cis*-PMMA and the af molecular conformation



**Fig. 10** *cis*-PMMA and the **af** molecular conformation

positive or negative charges interacting is clearly less than the attraction from opposite charges and the van der Waals interaction.

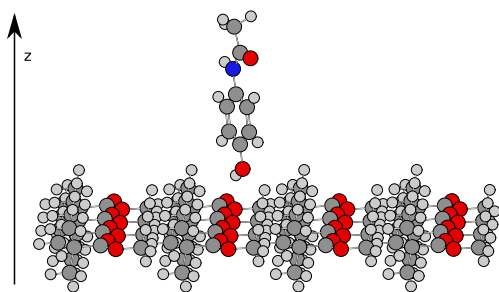
Three of the seven polymer orientations have a surface containing a combination of methyl group and one of the ether oxygens, *cis*-PMMA3, -4, and 6. When the carboxy oxygen, atom number 16 in Fig. 1, dominates the surface, the flat orientations of both conformations, orientation 1 and 2, have the energy minimum at distances longer than 2 Å. The sideways, orientation 5 and 6, and the vertical orientations, orientation 3 and 4, have energy minimum between 1.3 and 1.6 Å. When the surface is a combination of methyl group and the ether oxygen, atom number 15 in Fig. 1, all the orientations have the minimum energy approximately 0.5 Å closer to the surface. This effect is a result of the carboxy oxygen having a lower charge than the ether oxygen, and the repulsive forces between the negatively charged atoms in the molecule and the oxygen at the surface is thereby increased.

Further, the relative stability of **ac5** and **ac6** is reversed on the *cis*-PMMA4 surface covered with methyl groups and ether oxygens, compared to the situation with the molecules on the *cis*-PMMA3 and -6 surfaces cover with methyl groups and carboxy oxygens. In Fig. 12, the molecules are shown on the *cis*-PMMA3 and -4 surfaces. On *cis*-PMMA3, both orientations are able to match positive charges in the molecule with negative charges in the polymer, and vice

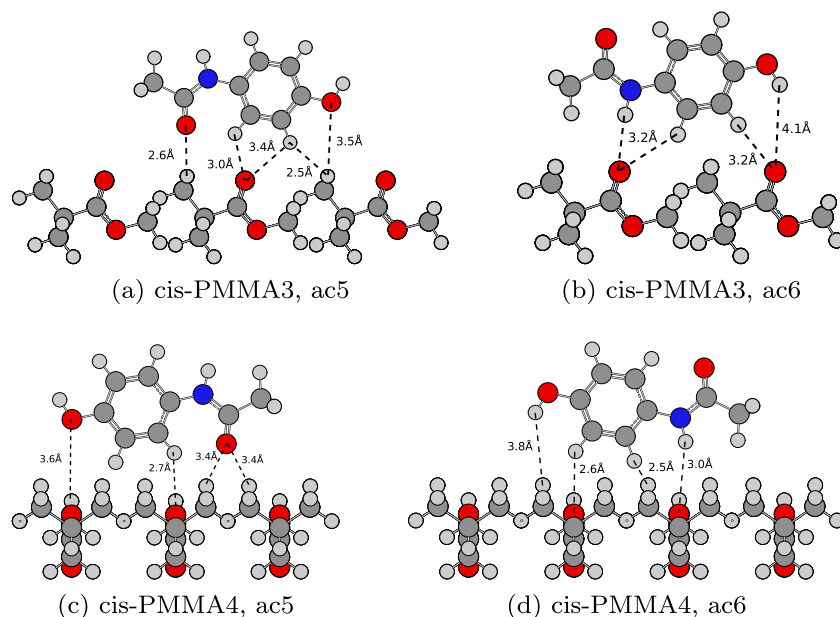
versa. This is not to the same extent possible on the *cis*-PMMA4 surface, where negative charges near the surface are favored. The conformation **ac5** has thereby a clear advantage and has an energy 0.16 eV lower than **ac6** on this surface. The hydroxy hydrogen affects the relative stability of the orientations 5 and 6 on the two surfaces. On *cis*-PMMA3, the **af5** conformation has lower energy than **af6**, which is the opposite of the **ac** conformation, and the energy is not reduced as much when going to the *cis*-PMMA4 surface. The energy of **af6** is reduced going from *cis*-PMMA3 to -4, which is the opposite of **ac6**. Thus, though no direct hydrogen bonds are observed, the position of the hydrogen is important.

When methyl groups are dominating the surface, *cis*-PMMA2 and -5, the flat orientations have energy minima at 1.5 and 2.0–2.2 Å. The sideways orientations reach the lowest energies between 0.9 and 1.0 Å when the surface is composed of *cis*-PMMA2, while it is reached between 0.5 and 0.6 Å when composed of *cis*-PMMA5. The energy of the flat orientations is 0.2 eV lower on *cis*-PMMA2 compared to *cis*-PMMA5. This is the result of a closer packing of the surface-methyl groups, and thereby greater van der Waals and Coulomb contributions. When less densely packed, as in *cis*-PMMA5, the sideways oriented molecules can get closer to the surface.

The *cis*-PMMA1 has both oxygen exposed at the surface alongside with the methyl groups. In this orientation, one methyl group is pointing “up” from the surface, and leaving long gaps in the surface. The vertical- and sideways-oriented molecules are able to fit into these, hence the short distance for the minimum energy, (Figs. 8a and 9a). This polymer orientation results in the lowest energy for all orientations in both molecular conformations. For the vertical and sideways orientations, this can be explained as the molecule being lowered into the gap and interacting with the methyl group at the same time. Hereby, the part of the molecule furthest away from the surface has increased interaction as well. The energies of the flat orientations are approximately the same as when *cis*-PMMA2 is used. The low energy arises mainly

**Fig. 11** The voids on the *cis*-PMMA1 surface and a **ac3** molecule in the void

**Fig. 12** The **ac** molecular conformation in orientation 5 and 6 on the *cis*-PMMA3 and -4 surfaces

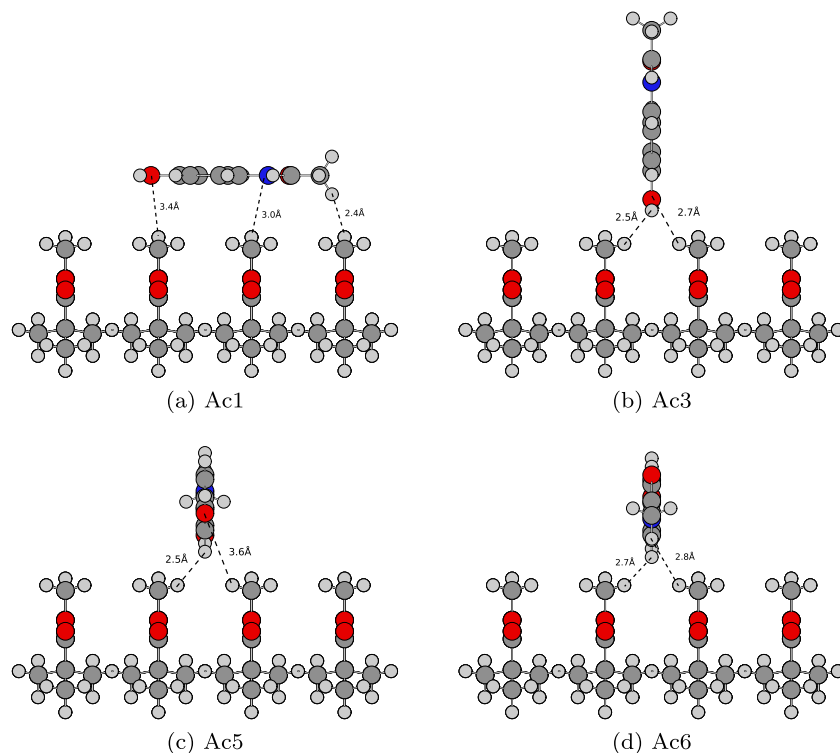


from the methyl group interacting with molecule, and less from the interaction with the oxygen atoms.

The *cis*-PMMA7 orientation resembles the real PMMA surface best of the polymer orientations investigated. Here, the same order of interaction is observed as for the other orientations. The molecule–polymer orientations are shown in Fig. 13 for **ac1**, **ac3**, **ac5**, and **ac6**. Only the terminating methyl group of the side chain is exposed to the surface, thus no bonding is possible between acetaminophen

and the oxygen atoms in the polymer. The formation of a hydrogen bond between either the hydroxy- or the amide hydrogen and the ester in the polymer would have been a guess on a strong PMMA–acetaminophen interaction, but when the surface is covered with methyl groups, this is not possible. Instead, the interaction is governed primarily by van der Waals interactions. In the case of the molecule being in vacuum, it is more energetically favorable to be on the surface.

**Fig. 13** *cis*-PMMA7 and the **ac** molecular conformation in orientation 1, 3, 5, and 6

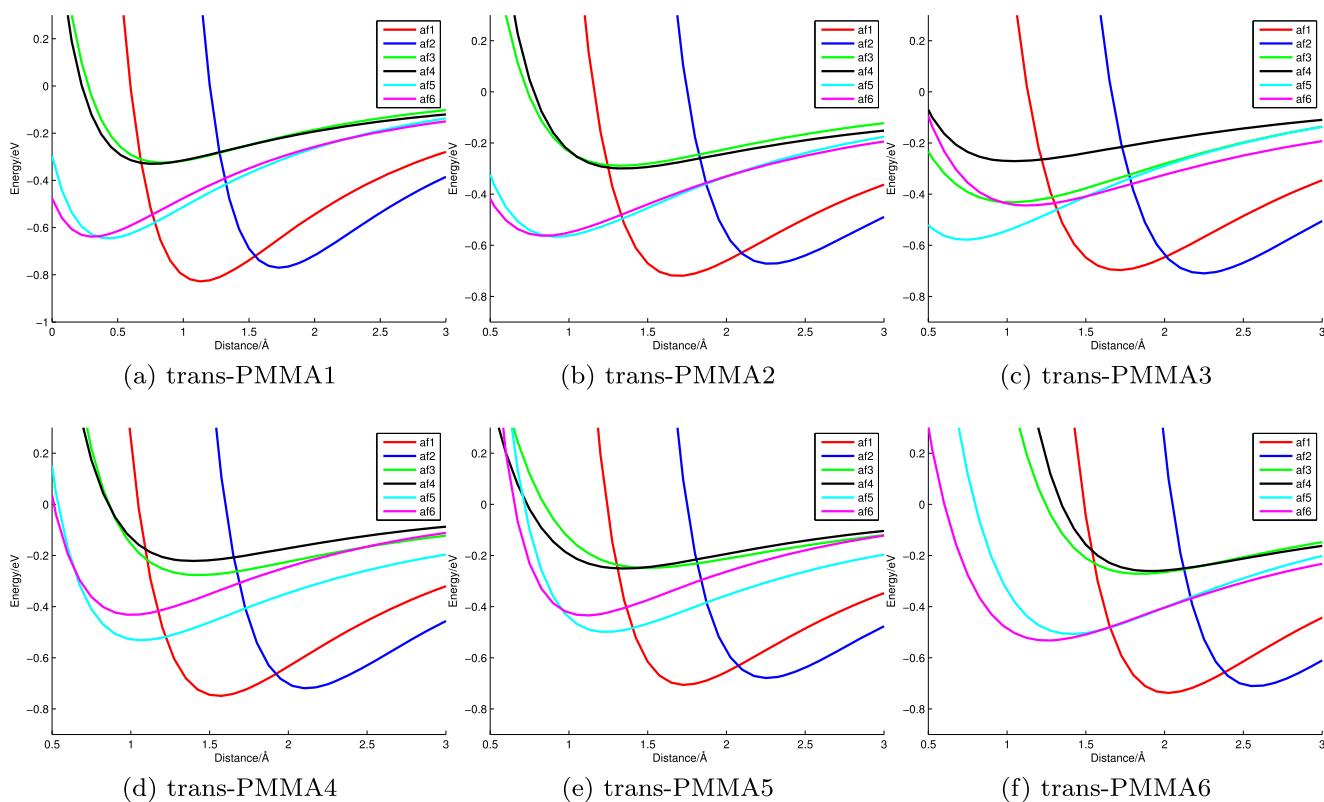


**trans-PMMA** The energies of the **af** and **ac** conformations in the six orientations nearing the *trans*-PMMA surface are shown in Figs. 14 and 15. As before, the lowest energy is obtained by the flat orientations at distances of 1 Å to 2.5 Å from the polymer surface. The sideways orientations are the third and fourth most stable orientations, and the least stable orientations are the vertical. The two sideways orientations behave very similarly when the surface consist of *cis*-PMMA, but when the surface is *trans*-PMMA, this is not a valid assumption. For the **af5** and **af6** orientations near the *trans*-PMMA3 surface, Fig. 14c, the energy of **af5** is 0.2 eV lower than that of the **af6**. In addition, the energy minimum of **af6** is at 1.1 Å, while the minimum of **af5** is at 0.7 Å. This could be an artifact from the grid-based search, but since the starting positions of the two orientations are identical, and they are rotated and translated the same, this is not a likely explanation. The reason could be an interaction between the molecule and the polymer surface. The sideways orientations seems to behave similarly in the rest of the *trans*-PMMA orientations.

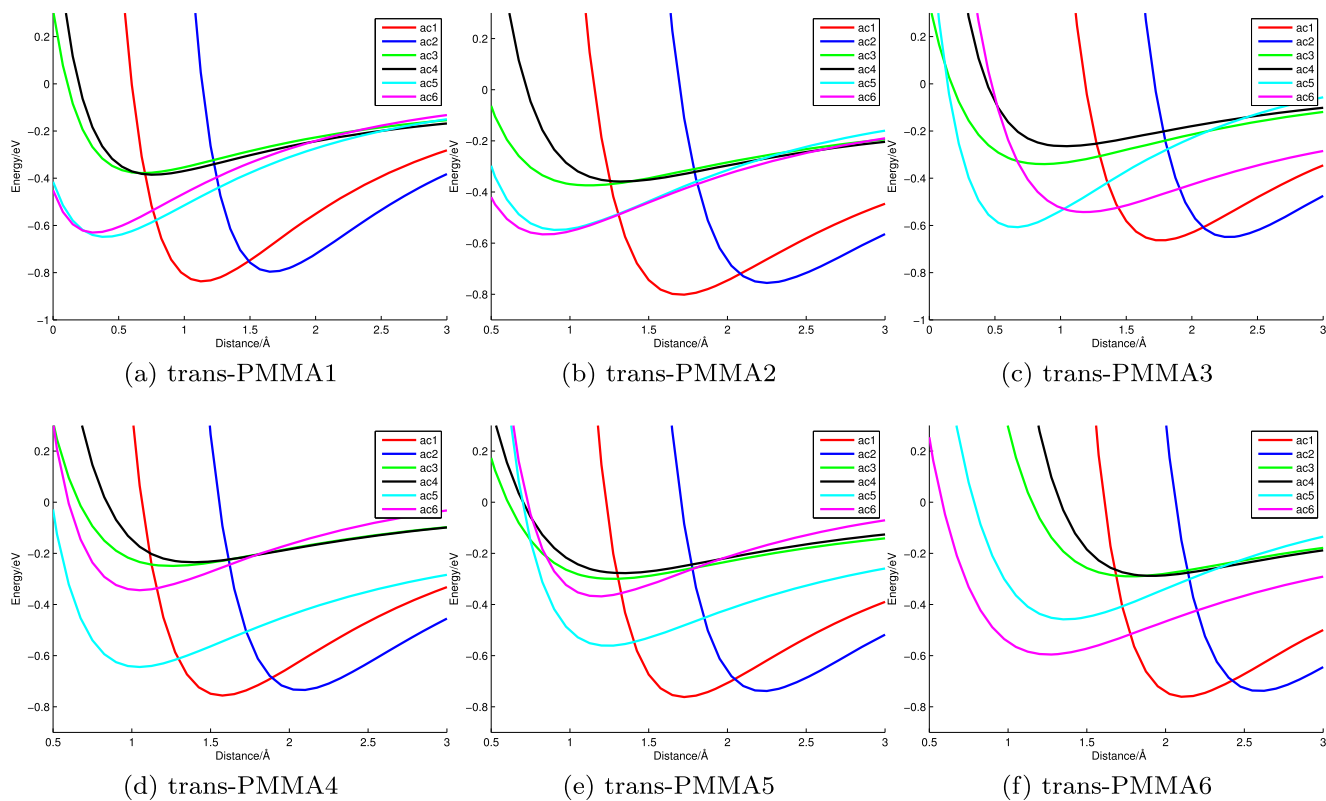
For the **ac** conformation, the lowest energy of the molecule in the **ac** conformation nearing the *trans*-PMMA surface is obtained by the flat orientations, followed by the sideways, and last the vertical orientations. The two sideways orientations behave very similarly when the surface consists of *trans*-PMMA1 and *trans*-PMMA2.

When they are approaching the *trans*-PMMA3 surface, the energy of **ac5** is about 0.03 eV lower than that of the **ac6** orientation, but the minimum energy is also found 0.5 Å further away from the surface. The two energy curves have different trajectories, which may imply that **ac5** forms a stronger bond when close to the polymer in this orientation. In addition, **ac5** and the flat conformations have almost the same energy.

In Fig. 16, the two sideways orientations at the *trans*-PMMA3 surface are shown at the energy minimum. From the picture, it is clear that the two molecules are rotated 90° compared to one another. The **ac5** molecule can get closer to the surface than **ac6**, since the distance between the carbonyl-oxygen atoms is wider in one direction than in the other (Fig. 16a and c). When the molecule is closer to the surface, the energy contribution, negative as well as positive, is increased from the Coulomb and Lennard–Jones potential. The **ac6** molecule seems to form interactions to the polymer through the amide hydrogen, the distance being 2.7 Å to nearest polymer oxygen, and a benzene hydrogen, the distance being 3.0 Å to the nearest polymer oxygen (Fig. 16d). For the position of **ac5**, one could argue that a weak localized interaction is formed between the hydroxy hydrogen and the nearest polymer oxygen; the distance is 3.3 Å, see Fig. 16b. Another reason is that the negatively charged carbonyl-oxygen in **ac5** is furthest away from two

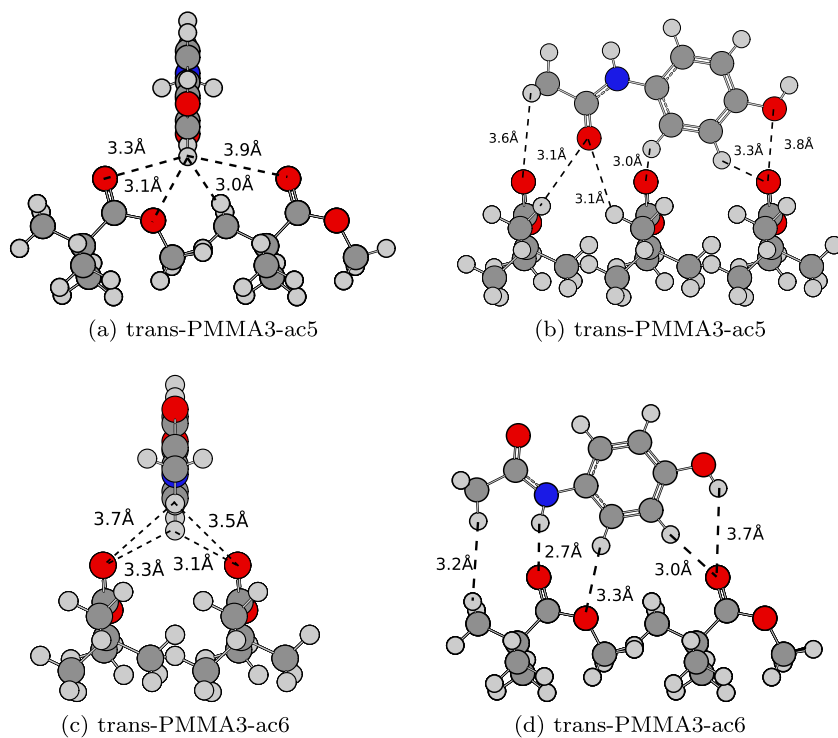


**Fig. 14** *trans*-PMMA and the **af** molecular conformation



**Fig. 15** *trans*-PMMA and the ac molecular conformation

**Fig. 16** *trans*-PMMA3 and the ac5 and ac6 molecular conformation and orientation



similarly charged oxygen atoms in the polymer. What is observed is probably a combination of both effects.

The orientation of *trans*-PMMA6 has the surface covered by a combination of oxygen atoms and the terminating side-chain methyl groups (Fig. 16f). Here, the relative stability of **ac5** and **ac6** is reversed compared to the other polymer orientations, since **ac6** has weakly positively charged hydrogen atoms near the surface, while **ac5** has the negatively charged oxygen atoms in that position. The result is that **ac6** is 0.2 eV lower in energy than **ac5**.

When the surface consists of *trans*-PMMA4 and *trans*-PMMA5, the energy minimum of **ac6** and **ac5** is at the same distance from the surface. The energy minima of **ac6** is 0.3 eV and 0.2 eV higher than **ac5**. The reason for this behavior is that in both polymer orientations the surface is covered by methyl groups and thereby hydrogen atoms (Fig. 6d and e). The hydrogens are all weakly positively charged, and the molecular orientation having negatively charged atoms closest to the surface obtains the lowest energy.

## PVA

The PVA monomer is only considered in one conformation, since the carboxy oxygen is close to the surface, i.e., not covered from the surface by the methyl group. The PVA orientations, Fig. 17, can be divided into three subgroups, each containing two orientations with similar features: PVA1 and -2 have a vertical orientation, and the surfaces are covered by methyl groups. PVA3 and -4 have sideways orientation, and the surfaces consist of a combination of methyl groups and either the carbonyl oxygen or the ether oxygen. PVA5 and -6 have a flat orientation, and the resulting surfaces consist of methyl groups and both oxygen of the polymer side chain.

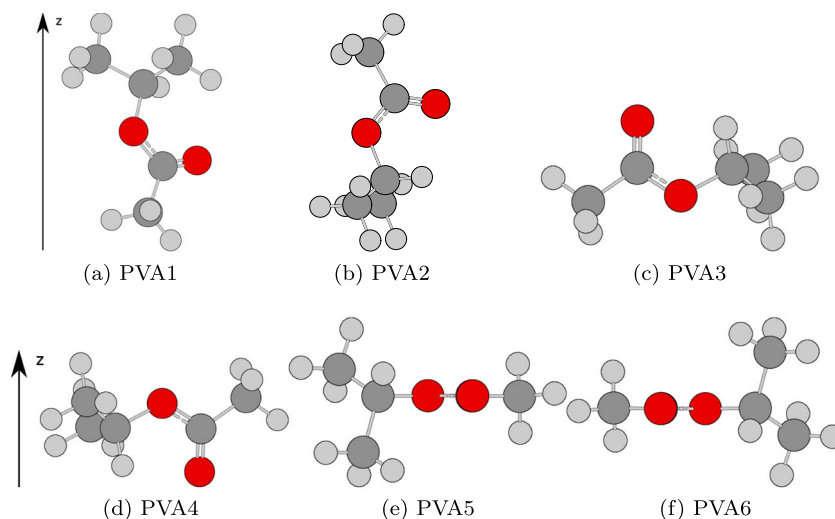
In Figs. 18 and 19, the energies of the orientations of **af** and **ac** are shown. As in the case of the PMMA, the orientations of the molecule in the flat conformations, **af** and **ac**, have the lowest energies. The flat orientations are followed by the sideways orientation, and lastly the vertical orientation.

The surfaces made of PVA1 and -2 are dominated by the methyl groups, and thus the relative stability of the acetaminophen orientations is expected to be the same. However, the electrostatic contribution from the atoms beneath the surface do play a role: The energy of **af5** is raised 0.25 eV, while the energy of **af6** is lowered 0.05 eV going from PVA1 to -2. Especially the negatively charged oxygen atoms in the molecule and polymer repel one another. Thus, the energy of **af5** is lowered when the polymer oxygen atoms are closer to the surface. The same effects are seen for **ac** orientations.

In Figs. 20 **ac5** and **ac6** are shown at the distance and orientation of the sideways **ac** molecules on PVA2 surface obtained from the energy minimization. The polymer–molecule interactions of PVA2-**ac5** and PVA2-**ac6** are almost identical, in relative orientations and intermolecular distances. This supports that the energy is determined, not as much by the first layer of atoms, as the location of the oxygen atoms.

The PVA3 surface is dominated by carbonyl oxygens, atom number 17, while the PVA4 surface is dominated by the ether oxygen, atom number 11, and methyl groups. The effect of the carbonyl oxygen atoms on the surface is that the minimum energies of **af** are at distances longer than 1.5 Å. Further, the energy is increased by approximately 0.1 eV for all orientations (except 3) going from PVA4 to -3. The minimum energies are still at distances longer than 1.5 Å when the **ac** conformation is used, and increased when going from PVA4 to -3. The energy of **ac6** is increased

Fig. 17 PVA orientation



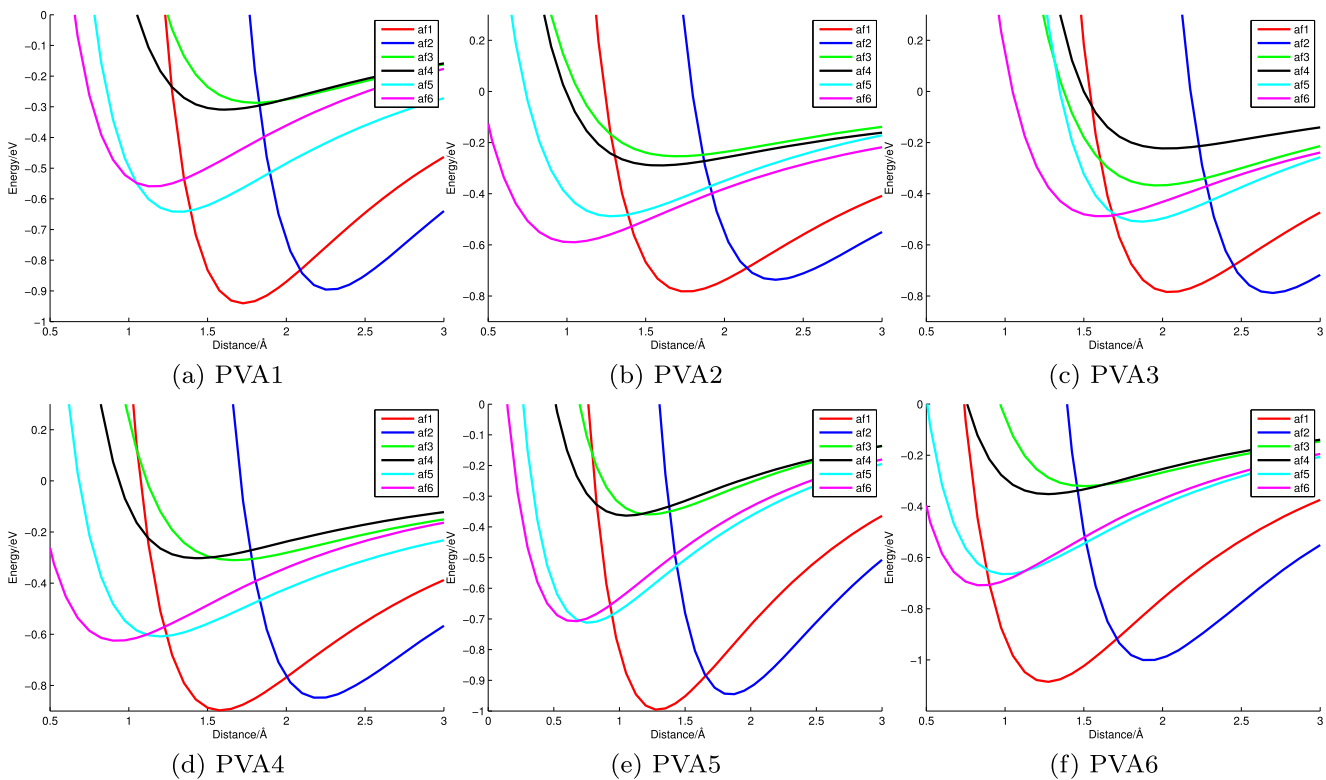


Fig. 18 PVA and the af molecular conformation

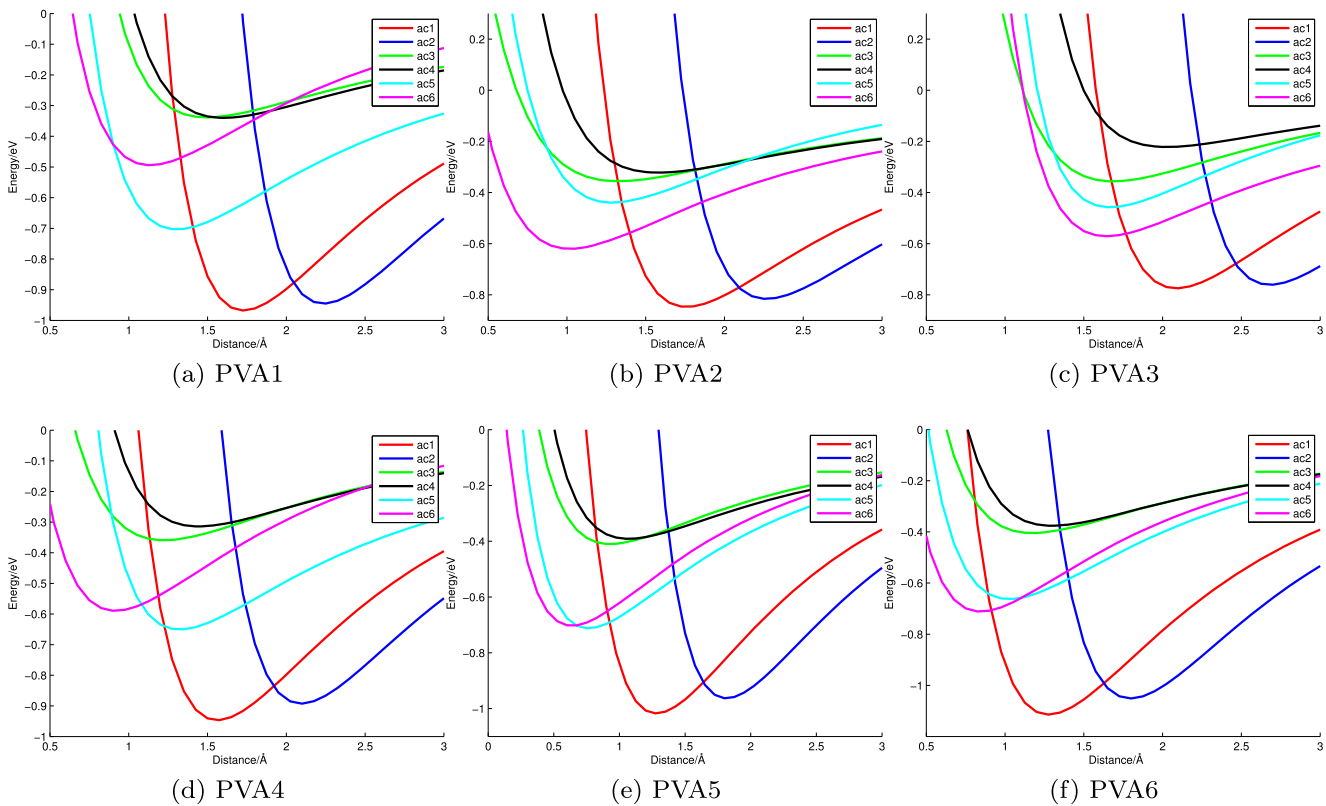
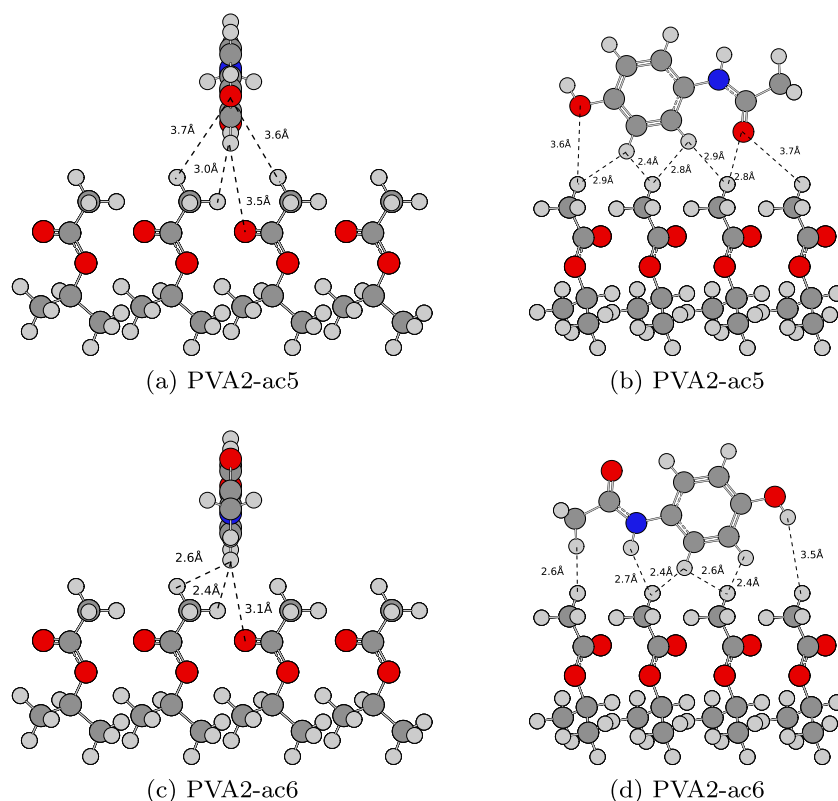


Fig. 19 PVA and the ac molecular conformation

**Fig. 20** PVA2 and the bf ac molecular conformation

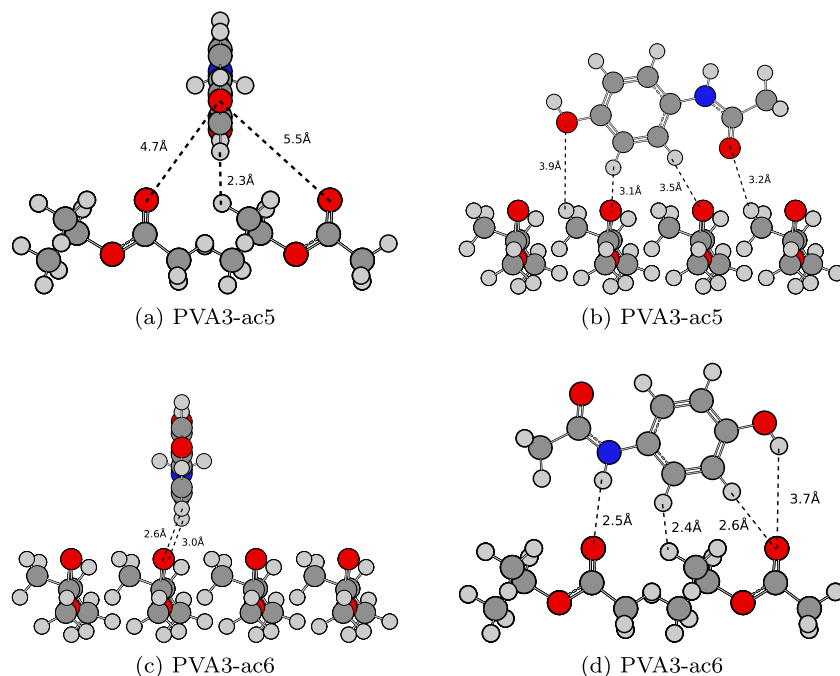
very little, around 0.03 eV, while the energy of **ac5** is increased by 0.2 eV. This is due to **ac6** having the positively charged hydrogen atoms toward the surface, while **ac5** has the negatively charged oxygen atoms in that direction.

In Figs. 21 and 22, we show the positions of the **ac5** and **ac6** molecules on the PVA3 and -4 surfaces, at the energy minimum distance. On the PVA3 surface the two orientations reaches the minimum energy at an orientation perpendicular to one another. By positioning like this, **ac5** is furthest away from the polymer atoms, and **ac6** is close to the same. From the geometry we see that the reason for the lowered energy of **ac5** on PVA4 compared to PVA3 is a result of the carbonyl oxygen interacting with a methyl hydrogen, and a benzene hydrogen interacting with an oxygen in the polymer.

Whether the carbonyl oxygen is close to the surface or not plays an important role in the relative stability of **ac5** and **ac6**, as demonstrated by the PVA1 and -2, and PVA3 and -4. When the surface is made of PVA3 and -4, the energy of all the molecular orientations is raised going from 3 to 4. The molecule–polymer distance is increased for all **af** orientations; all but **af5** is about 0.3 Å further away, while **af5** is 0.5 Å further away. The reason for the increased distance is that **af5** forms a strong interaction between amide oxygen and a hydrogen in the polymer. In Figs. 21 and 22, **ac5** and **ac6** are shown on the PVA3 and -4 surface from two different angles. On the PVA3 surface,

the two molecules are directed perpendicular to one another on the surface at the minimum energy. The conformation **ac5** maximizes the distance between oxygen atoms in the molecule and polymer, while the **ac6** conformation optimizes the hydrogen-oxygen distance. On the PVA4 surface, **ac6** is oriented to minimize the distance between hydrogen atoms in the molecule and oxygen in the polymer, similar to what is observed on the PVA3 surface. The conformation **ac5** on the other hand, is oriented differently on this surface compared to PV3. Here, the molecule is placed so the oxygen atoms are near the surface of the hydrogen atoms, and the molecular hydrogen atoms are near the surface of the oxygen atoms.

On the surface of the last set of polymer orientations, the orientations of **ac** and **af** behave very similarly on the two surfaces. In Fig. 23, the orientations of **ac5** and **ac6** on the PVA6 surface are shown. The orientation of **ac6** in the gap is also representative for **ac5** and **ac6** on the PVA5 surface. As on the PVA3 surface, **ac5** forms a strong interaction between the amide oxygen and a hydrogen on PVA6 surface. Further, the benzene hydrogen atoms interact with the oxygen atoms in the polymer, and the hydroxy group interacts with the other methyl group of the polymer. This interaction is not formed on the PVA5 since the methyl group sticking out of this surface would elevate a molecule in a corresponding position and the energy contribution from the other atoms would be smaller.

**Fig. 21** PVA3 and the ac molecular conformation

## PVA and PMMA

The lowest energy at all surfaces is obtained by the flat conformations, followed by the sideways and vertical orientations. The energy of the flat orientations on the *cis*-PMMA surface is between -0.95 and -0.6 eV, where the highest energy is obtained on the surface resembling the experimental surface best. The sideways orientations have

an energy between -0.4 and -0.8 eV, while the highest energy is obtained by the vertical orientations between -0.2 and -0.4 eV. The energy of all the conformations is generally 0.2 eV higher when the *trans*-PMMA polymer is used. The reason is the exposed carbonyl oxygen, which is strongly negatively charged and thereby repels the negatively charged atom in the molecule. The combination of Lennard–Jones and Coulomb interactions only include

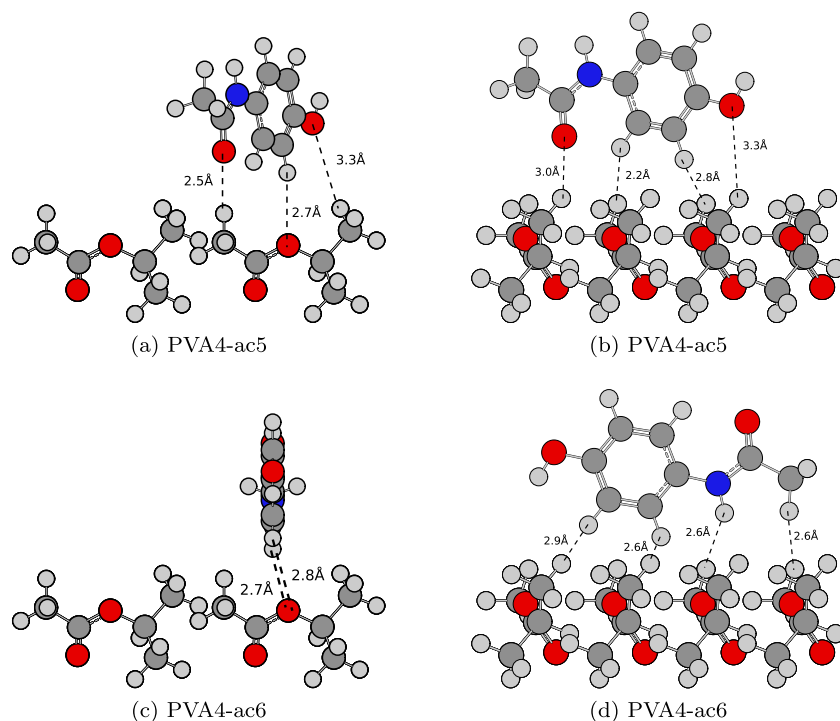
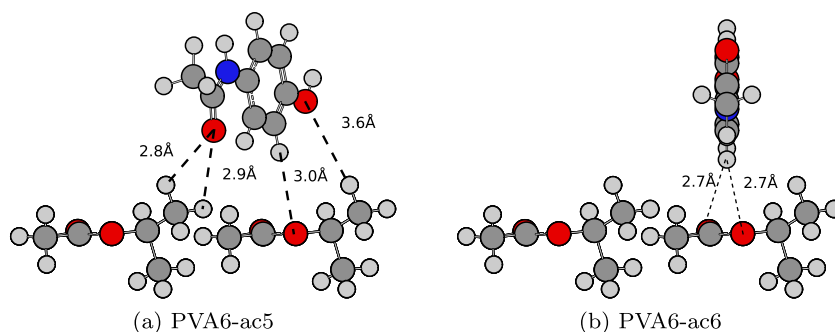
**Fig. 22** PVA4 and the ac molecular conformation



Fig. 23 PVA and ac5 and ac6



electrostatic and van der Waals forces, the effects of bonds, and dipole and multipole interactions are thereby not accounted for.

Despite a lower number of atoms in the PVA surface, compared to PMMA, it has overall lower interaction energies for the flat conformations. The energy of the flat orientations on the PVA surfaces range between -0.8 and -1.2 eV, while the same conformations have energies between -0.6 and -1.0 eV on the PMMA surfaces. This may arise from the polymer units being closer packed, due to the smaller size of the monomeric unit. The shorter distance between the charged atoms increases the Coulomb and to some degree the van der Waals contribution to the energy contribution, negative as well as positive.

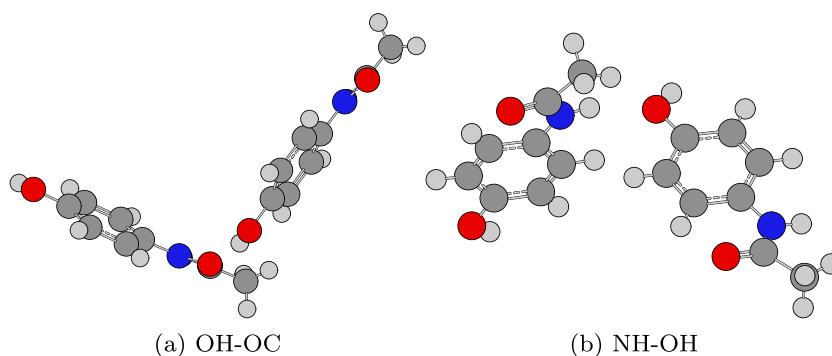
## Results and discussion

We determine the hydrogen bonding energies in order to establish whether the interaction energies are high or low. In the monoclinic and orthorhombic crystals, each molecule forms two hydrogen bonds. In Figs. 24 and 25, the molecular dimers are shown. The interaction energy is determined as:

$$E_{Hbond} = E_{dimer} - 2 \cdot E_{monomer} \quad (7)$$

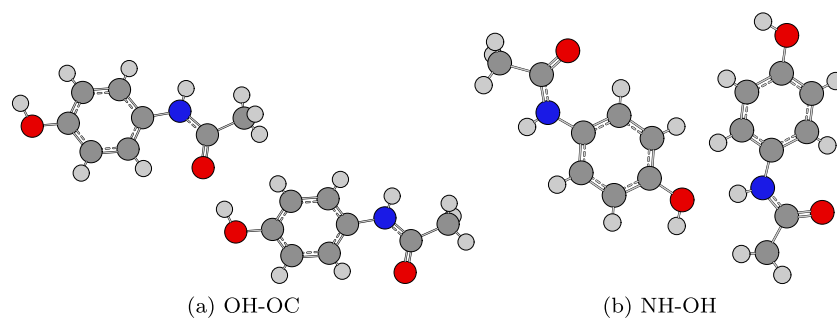
and the interaction energies range between -0.14 and -0.36 eV when we perform electronic structure calculations using the CAM-B3LYP functional with the cc-pVQZ basis set.

Fig. 24 Dimers in the monoclinic crystals



In Table 4, the energies are listed in eV for other basis sets as well. We compare the results from this investigation with our previous work utilizing a heterogeneous dielectric solvation model [25] and we perform the comparisons with the flat conformations used in both models. The lowest energies in vacuum obtained with the two models are -0.11 and -1.1 eV, for the heterogeneous dielectric solvation model (HDSM) and Coulomb-van der Waals model (CvdW), respectively. The CvdW model has the advantage of having energy contributions from either 2000 or 1700 atoms located in the surface of the polymer, depending on whether PMMA or PVA is used, while the HDSM model only has 20 induced charges in the solid. This will of course influence the energy but the lower number of charges in the HDSM model leads to an easier approach and it still enables to mimic the impact in the polymer of the molecule.

When the molecules in the **af** conformation are subjected to the HDSM model, the lowest energy, -0.055 eV, of **af** is obtained by orientation 5, **af5**, the sideways orientation pointing the carbonyl oxygen (O(20)) toward the surface. The energy of the **ac** conformation in the same orientation, **ac5**, is -0.05 eV, but more importantly the flat orientation 2 has an energy of -0.08 eV near the surface. The increased overall dipole moment of **ac** compared to **af** results in a change in the relative stability of the orientations 2 and 5. When the CvdW model is used, the lowest energy of both conformations are the flat orientations 1 and 2. Due to being slightly tilted, the orientation 2 has an energy minimum

**Fig. 25** Dimers in the orthorhombic crystals

further from the surface than orientation 1. The minimum energies range between -0.6 and -1.1 eV, depending on the polymer used and the orientation of the polymer.

The HDSM model has been expanded to include the solvent as a second dielectric medium. Here, the lowest energies are obtained by orientation 6, having an energy of -0.13 eV and -0.155 eV in the **af** and **ac** conformation. The orientations having charged atoms near the solvent surface are favored energetically, since the dielectric constant is higher in the solvent than in the solid. The model provides insight into the geometry of the solvated molecules at the surface. The solvent has a higher dielectric constant than the polymer and is therefore expected to interact more strongly with the molecule. In the CvdW model, a similar effect to what is observed in the HDSM model is expected since the density of atoms in the surface influence the energy. The experimental density of solvent and polymer may provide some insight and the density of water is  $1.0\text{g}/\text{cm}^3$ , while PVA and PMMA have densities of  $1.19\text{g}/\text{cm}^3$  [34] and  $1.18\text{g}/\text{cm}^3$  [35]. This corresponds to an average atomic density of  $0.1\text{atoms}/\text{\AA}^3$  in all three materials. Thus, the number of charges within a given radius is the same when the molecule is in solution and near the surface. The difference between solvent and solid in the CvdW model is the mobility and size of the charges.

From the HDSM model, we know that the sideways orientations will have a more pronounced role when including the solvent. The polymer surfaces mainly or only contain methyl groups, like *cis*-PMMA7, and will of course interact weaker with the molecule in a solvated situation. It is expected that a sideways orientation will have the lowest

energy, but a vertical orientation may have even lower energy, if the interaction with the solvent is sufficiently strong.

Though none of the models are perfect, they each have an advantage: The CvdW model does account for the structured surface of the polymers, while, on the other hand, the HDSM model includes solvent and induces charges in the surrounding dielectric media. A combination of the two models may provide an insight into the mechanism of heterogeneous nucleation.

The energies determined by the CvdW model range between -0.2 and -1.1 eV and compared to the dimer energies in the crystal, the molecule–surface interaction energies are high and may be overestimated. The flat orientations on the polymer surfaces would easily outperform the intermolecular hydrogen bonds. The hydrogen bonds are not the only intermolecular interactions in the crystal, the  $\pi - \pi$  stacking is important as well. Nevertheless, the energies indicate that the surfaces do interfere with the nucleation event.

The model predicts that in vacuum the most occurring orientation on both polymers ought to be the flat one and the work done by Matzger [23] has shown that this is only the case when the orthorhombic crystals are grown. During this work, sideways and flat-vertical orientations were observed and from the calculations we have shown that especially the PVA surface should induce the flat orientation. Since no experimental investigations to our knowledge have been done to investigate the vacuum nucleation on PVA, we are not able to verify the result. On the PMMA surface, a mixture of multiple orientations was observed by Matzger [23], so even in vacuum it is not as simple as the CvdW model.

The most stable solvated orientation is expected to be a sideways orientation. A flat orientation would indicate a very strong interaction and is only observed on the horizontal PMMA and PVA surface, and on one vertical PMMA surface. In the case of the horizontal surfaces, the probability of an already-formed nuclei attaching to the surface is high. This could also happen at the vertical surface but it is very unlikely. Thus, the orientations on the horizontal surface are left out in the following.

The PVA surface, which according to the calculations interacts stronger with the molecule than the PMMA surface,

**Table 4** The interaction energies of the dimers in the monoclinic and orthorhombic crystals

Monoclinic	cc-pVDZ	cc-pVTZ	cc-pVQZ
1: $E_{OH-OC}$ / eV	-0.3861	-0.3005	-0.2800 eV
2: $E_{NH-OH}$ / eV	-0.3220	-0.1924	-0.1577 eV
Orthorhombic	cc-pVDZ	cc-pVTZ	cc-pVQZ
1: $E_{OH-OC}$ / eV	-0.4781	-0.3808	-0.3557 eV
2: $E_{NH-OH}$ / eV	-0.2383	-0.1627	-0.1372 eV

ought to direct a more flat orientation. The orientations seen are sideways or somewhere between vertical and flat. The sideways orientations are third and fourth most stable in vacuum, and they are expected to have the lowest energy when solvated, since the surrounding solvent will solvate this configuration better as seen in ref. [25] using a heterogeneous solvation model. The vertical-flat orientations have not been investigated in the computational studies, but may be rationalized as a compromise between the flat and vertical orientations. The flat orientation interacts strongly with the surface since all the atoms are close to the surface and not exposed to the solvent. On the other hand, the vertical orientation interacts with the solvent since the molecule sticks out into the solvent.

On the PMMA surface, the most common orientation is sideways, as predicted by the IC model. For the surface to induce an orthorhombic crystal, the flat orientation has to dominate the surface. The kinetic factor in the sublimation experiment on the PMMA surface results in monoclinic crystals.

The molecular orientations on the surface are determined on the basis of the known crystal structures. The surface of the crystal probably has another molecular arrangement than the bulk. Thus, the molecular orientation on the interface between crystal and polymer surface may differ from the orientation on the experimentally determined crystal faces. A good assumption is that the often-observed molecular orientation is the actual orientation at the surface. This implies that though the flat orientations are rarely observed in the crystallographic planes, they may still be the orientations dominating the surface when the flat-vertical orientations are observed. The orthorhombic crystal is not seen, since the kinetics of the crystal growth allows the monoclinic crystals to form.

It was expected that the PVA surface would facilitate a growth of monoclinic crystals, while the PMMA surfaces are able to induce orthorhombic crystals. Since the monoclinic crystals are obtained easily, one would expect the molecules to interact less with the PVA surface than the PMMA surface. From the computational investigations, it is obvious that the PVA surface interacts stronger with the molecule, in contrast to what was expected. This further supports that the crystallization event is not solely determined by the molecule–surface interaction.

## Conclusions

Polymorphic selection of acetaminophen on polymer surfaces has been investigated computationally. The computationally CvdW model is able to differentiate between polymer surfaces and molecules were found to interact more strongly with the PVA surface than with the PMMA surface.

This is in contrast to expectations, since the alleged findings of orthorhombic crystals on the PMMA surface suggest a strong molecule–polymer interaction.

Detailed mechanistic understanding of the complexities of nucleation requires additional work. Developments of the theoretical models should include structured solvent descriptions, and more importantly, address the kinetics of aggregations.

We have clearly shown that an atomistic model for the interactions between acetaminophen and a polymer surface is a complicated issue and all the possible arrangements of the molecule and the polymer surface have to be taken into account before one is able to determine the most favorable choice of polymer and molecular conformation. For the present model, we do observe that we are missing the outer solvent that surrounds the attached acetaminophen to the polymer surface.

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