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Experimental and theoretical investigation of the complexation of methacrylic acid and diisopropyl urea

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ABSTRACT

The present paper explores the complexation ability of methacrylic acid which is one of the most abundant functional monomer for the preparation of molecularly imprinted polymers. Host-guest interactions and the mechanism of complex formation between methacrylic acid and potentially genotoxic 1,3-diisopropylurea were investigated in the pre-polymerization solution featuring both experimental (NMR, IR) and in silico density functional theory (DFT) tools. The continuous variation method revealed the presence of higher-order complexes and the appearance of self-association which were both taken into account during the determination of the association constants. The quantum chemical calculations – performed at B3LYP 6-311++G(d,p) level with basis set superposition error (BSSE) corrections – are in agreement with the experimental observations, reaffirming the association constants and justifying the validity of computational investigation of such systems. Furthermore, natural bond orbital analysis was carried out to appraise the binding properties of the complexes.

1. Introduction

Molecular imprinting is a versatile technique for the preparation of intelligent materials exhibiting selective molecular recognition towards a template [1]. The self-assembly of the template molecule and the functional monomer in the pre-polymerization solution yields selective binding cavities with complementary functionalities and topographies to the template. Imprinting is usually based on reversible non-covalent interactions, and one of the most common functional monomers is methacrylic acid [2–5]. This article deals with the pre-polymerization complex of methacrylic acid (MAAH) and potentially genotoxic 1,3-diisopropylurea (IPU) template which were previously used for molecular imprinting as functional monomer and template, respectively (Fig. 1) [6]. In order to better understand the complexation mechanism, multiple methods were applied to investigate the system (NMR, IR and DFT).

NMR titration, a relatively common method in host-guest chemistry, was used to determine binding constants where host and guest are mixed in different ratios and the NMR spectrum of the mixture is measured. NMR titration is often used to understand complexation phenomena in macrocycle chemistry [7–9], molecular imprinting [10,11], and receptors [12,13]. Due to fast-exchange correlation the NMR signals of the complexes and the initial compounds do not appear separately but as their average. Both 1:1 and 1:2 complexes and self-association of the initial compounds were considered. Although the application of IR in the investigation of binding properties of weak complexes is limited, it can provide information about the vibrations at the binding site, thus giving additional proof for complexation.

In recent years parallel to the experimental methods, the interactions between the template and the functional monomer or the polymer were explored by various in silico methods [14–19]. In the earlier studies the statistical and the molecular mechanics/classical molecular dynamics studies are predominant and quantum chemical methods have only been applied in recent years due to rapid development in computational power. Most of the computational studies in the imprinting literature focus on rapid functional monomer screening. In this method semiempirical or simple Hartree-Fock techniques are employed in order to choose the most stable complexes, which are recalculated with density functional theory (DFT) methods. The ab-initio and DFT methods, which are applied in present article, are suitable for modelling the chemical interactions between the monomers and templates, describing their binding properties and the stability of the investigated complexes. The exact determination of equilibrium constants in condensed phases is, however, presently beyond the limit of these methods.

2. Experimental

2.1. Materials

1,3-Diisopropylurea (IPU) was kindly provided by Hovione FarmaCiencia SA (Portugal). The chemicals were of reagent grade or

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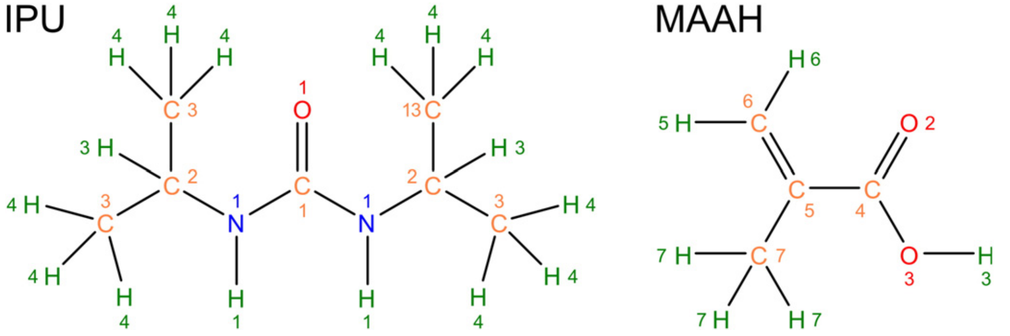

Fig. 1. Structure and atom numbering of IPU template (guest), MAAH functional monomer (host).

higher and used as received from Sigma-Aldrich. Anhydrous solvents were stored over molecular sieves.

2.2. Analytical methods

2.2.1. NMR and IR methods

The ^{1}H NMR spectra were recorded at 25 °C within a deviation of 0.2 °C. Chemical shifts (δ) are reported in ppm, with respect to the solvent peak of deuterated chloroform being 7.26 ppm [20]. The following abbreviations are used in the discussion: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, and bs = broad singlet. The solvent was kept under molecular sieves and handled under inert atmosphere in order to avoid contamination of the system with water which disrupts the intramolecular hydrogen bonds. For the self-association NMR experiments 1 mM, 2.5 mM, 5 mM, 7.5 mM, 10 mM, 20 mM, 30 mM, and 40 mM IPU working solutions were prepared in $CDCl_3$. Additionally, Continuous Variation Method (CVM) was also performed for obtaining the stoichiometry of the complex. During the CVM, the host/guest molar ratio was varied between 0 and 1 while their total concentration was kept constant at 20 mM. In CVM the host was MAAH. Furthermore, two sets of NMR titrations were carried out where IPU was titrated with MAAH: T1 (5 mM IPU) and T2 (10 mM IPU). In order to study the effect of concentration, T1 was performed from 0 to 2 equivalents of MAAH with respect to 5 mM IPU, while T2 was performed from 0 to 5 equivalents of MAAH with respect to 10 mM IPU. The solutions were agitated to dissolve the IPU and homogenise the solution and were always freshly prepared just prior to analysis. The room temperature Fourier transform infrared (FTIR) spectra of MAAH and IPU compounds and corresponding 20 mM IPU:MAAH (1:1) complexes were measured in DCM, in the 4000–400 cm^{-1} region at a resolution of 4 cm^{-1}.

2.3. Quantum chemical methods

Quantum chemical computations were carried out using Gaussian 03 suite of programs [21], using the Becke3-Lee-Yang-Parr exchange-correlation functional [22,23], in conjunction with 6-311++G(d,p) basis set. The B3LYP functional is a general functional was chosen to be accurate with more calculated properties and this functional was used in most of the previous DFT studies [24,25]. Diffuse functions in the basis set (denoted with ++) were chosen to obtain better results for the hydrogen-bonded systems [26,27]. The minimum character of the stationary points obtained by geometry optimizations was checked by vibrational frequency calculations. The solvent effects were considered implicitly by the polarizable continuum model (PCM) [28–30]. The solvation energies could be calculated only on the optimized geometries of the isolated structures, since the starting unequilibrated structures in most cases failed to converge with PCM. The other two investigated compounds – 1,3-diisopropyl-urea (IPU) and methacrylic acid (MAAH) – were built up manually. Three structures were considered both for IPU^{a,b,c} and *trans*-MAAH and *cis*-MAAH (Fig. 2) for the further calculations determining the lowest energy geometrical structure of the complexes. Due to the high number of possible conformers 24 initial IPU-MAAH complex structures were built up and optimized both for 1:1 and 1:2 complexes. Natural bond orbital (NBO) analysis [31] was performed to explain the binding properties of the complexes. The calculation of anharmonic frequencies as well as the usage of scaling factors was omitted, since the agreement between the measured and the calculated spectra was sufficiently good for most of the spectra even without considering these corrections. Due to the appearance of weak interactions (H-bonds), the calculated reaction energies were corrected utilizing the a posteriori counterpoise method of BSSE [32]. This error arises due to the finite basis sets which are centered on the atoms: the number of basis functions is different for the complex and the two initial compounds and the ghost orbitals can contribute to a larger decrease in the energy in the complex compared with the initial compounds. The computed geometries have been visualised using the GaussView 3.09 program.

3. Results and discussion

3.1. Effects of self-association and stoichiometry on complexation

The investigation started with Continuous Variation Method (CVM) experiments, where IPU mole fraction × Δδ (chemical shift change) is plotted as a function of IPU mole fraction. The points on this curve are proportional to the concentration of the complex assuming solely 1:1 complexation (for details see Supporting information 3.4). The results of the CVM are shown in Fig. 2. The global maximum of the fitted curve occurs at about 0.57 mole fraction of IPU. This corresponds to a

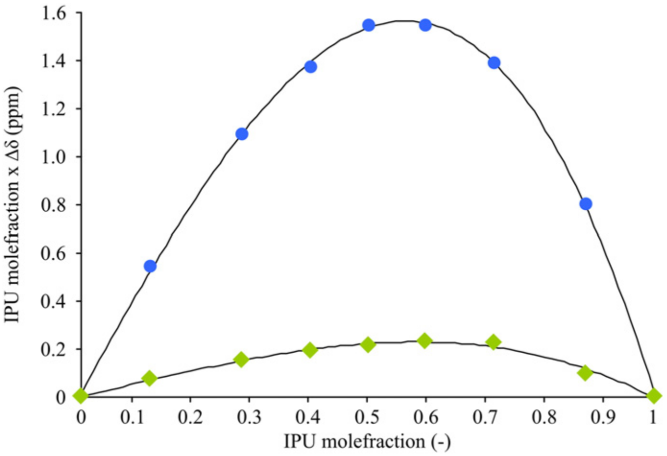

Fig. 2. Job plot of the IPU-MAAH complex, the blue dots and green squares are attributed to the H1 and H3 signals of IPU, respectively (for the numbering of atoms see Fig. 1); the total concentration IPU + MAAH was 20 mM.