Atomistic Simulations of Biomolecules at the Water-Amorphous Silica Interface: Application to Peptides and DNA Oligomers

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ABSTRACT

Realistic modeling of the behavior of biomolecules near the materials commonly used for biomedical device fabrication is required for their design and evaluation. Here we report the development of a practical scheme to integrate our previously developed model for the water-amorphous silica interface [Hassanali, Singer, *J.Phys.Chem.B*, 2007, **111**, 11181; Hassanali *et al.*, *J. Comput. Theoretical. Chem.*, 2010, **11**, 3456] with common biological force fields to treat biomolecules at this important interface. We then apply the methodology to study binding of the lys-trp-lys and glu-trp-glu tripeptides, and a DNA oligomer, at the water-silica surface. Mechanisms for binding of biomolecules at the water-amorphous silica interface are identified.

Keywords: nanofluidics, amorphous silica, biomolecule adsoprtion, molecular dynamics

1 INTRODUCTION

Understanding amorphous silica [1, 2], and its interaction with adsorbates from aqueous solution, is central to a broad range of technologies, including nanotechnology. Silica is the basic material for microchip-based DNA purification techniques [3, 4]. Recently, interest in the properties of adsorbates at the amorphous silica/water interface has been stimulated by applications in nanotechnology and, in particular, nanomedicine, where silica nanoparticles have found use in diagnostics and drug delivery [5–8]. Considerable effort has been invested in using silica nanochannels to stretch and sequence DNA [9, 10]. The importance of biomolecules at the water-silica interface in a variety of situations has prompted a number of fundamental investigations of the interactions of silica with nucleic acids [11–17] and with proteins [18–27]. It should be noted that silicon acquires an oxide coating in contact with aqueous solution [28, 29], so the water/amorphous silica is also quite relevant for silicon-based devices. Finally interaction of biomolecules with crystalline and amorphous silicates is key to understanding the widely varying toxicity of the different forms of SiO_2 [30, 31].

Nucleic acids and many proteins can have a substantial overall electric charge. The silica surface in contact with water is negatively charged at all but the lowest *p*H values. Overall electric charge of biomolecules and the surface accounts for gross trends, but binding of biomolecules to silica is not simply explained as "like molecules repel, unlike molecules attract." While a silica surface binds positively charged bio-molecules more strongly than negatively charged ones, even molecules with an overall negative charge like albumin [32–34] or nucleic acids [9–17, 35, 36] bind to untreated silica at *p*H values where the silica surface is negative. For example, binding of bovine serum albumin (BSA) at *p*H 7 was sufficient to affect the zeta potential of colloidal silica particles [33]. Also, in quartz crystal microbalance experiments, Wolny *et al.* confirmed that incubation of silica with BSA solutions at *p*H 7.4 and 10 mg/mL (a concentration typically used when BSA is employed to block non-specific binding to silica chromatographic media) produced a stable protein layer [37]. Furthermore, as mentioned above, binding of negatively charged DNA to silica has been measured in numerous experiments [11–17, 35, 36]. The studies of tripeptides presented here illustrate how both positively (lys-trp-lys) and negatively (glu-trp-glu) charged biomolecules can be stabilized at the amorphous silica/water interface.

2 INTERACTION MODEL

Our strategy to develop of a full model for biomolecules at the silica/water interface is to interpolate between representative *ab initio* fragment calculations. We interpolate in two senses. First, like many force fields, we assume that parameters for atoms in similar bonding situations are transferable. Secondly, we use standard Lorentz-Berthelot combining rules [38] to infer interactions where we have not generated quantum chemical data. The representative cases are a group of small probe molecules which contain functional groups often found in biomolecules – methane (CH_4), methanol (CH_3OH), ammonium (NH_4^+), acetate (CH_3COO^-) and benzene (C_6H_6) – whose energetics near several different fragments from the silica surface (Fig. 1) were investigated. This set of molecules included non-polar, polar, charged, and aromatic species. Nine combinations of probe molecules and silica fragments of various size were used to determine interaction parameters. All *ab initio* computations were performed with Gaussian program packages [39]. For all molecules brought up to the silica fragments except benzene, we em-

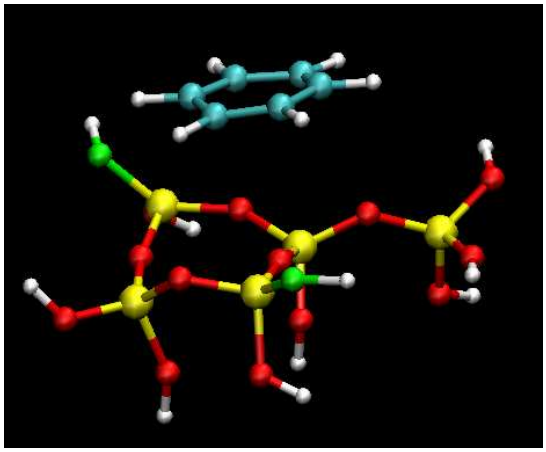

Figure 1: A silica fragment with a benzene probe molecule, one of the systems used in *ab initio* calculations. The colors used to represent different atoms in the fragment are red: oxygen, green: silanol oxygen, yellow: silicon, white: hydrogen.

ployed MP2 level [40–44] electronic structure theory with a 6-311G** basis set. We optimized each small molecule in contact with the silica cluster, and then varied the distance between the molecule and the silica fragment to generate a potential energy surface. Single point comparisons indicated that the 6-311G** basis set was adequate for these cases. However, for benzene-silica interactions we found that diffuse functions were needed, and the 6-311++G** basis was used in this case. Owing to the size of the benzene-silica

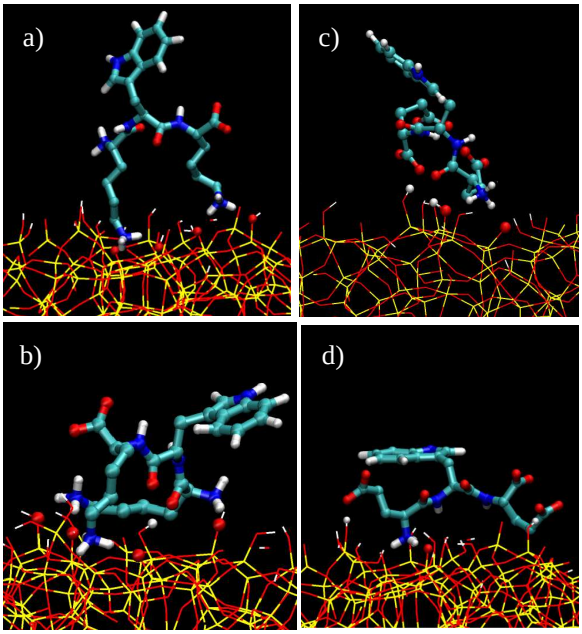

Figure 2: Snapshots of tripeptide binding to the silica surface sites. (a) KWK, two points of attachment (b) KWK, four points of attachment (c) EWE, two points of attachment (d) EWE, three points of attachment.

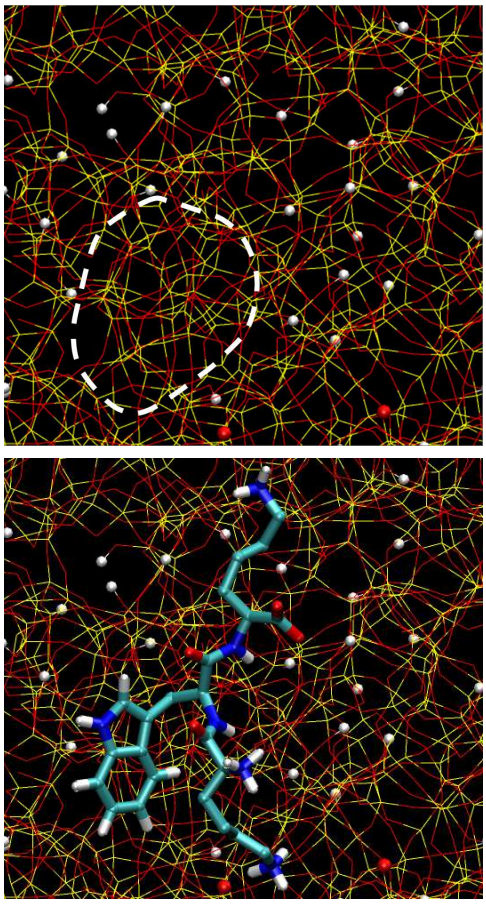

Figure 3: Snapshot of KWK tripeptide binding involving hydrophobic regions of the silica surface. The peptide is not shown in the top panel to reveal the nature of the hydrophobic binding region, which are indicated by dashed curves. The absence of silanol hydrogens (white atoms) and dissociated silanol oxygens (large red spheres) within the indicated regions confirms their hydrophobic nature. The same reigon with the bound peptide is shown in bottom panel.

system, we only obtained energies for an optimized binding configuration and separated fragments, i.e. a binding energy.

We optimized Lennard-Jones parameters for three atom types of the silica surface O_X,O_H,O_M (siloxane oxygen, silanol oxygen, and dissociated silanol oxygen) to achieve a best fit to the *ab initio* data when using Lorentz-Berthelot combining rules [38]. Detailed results and model parameters are given in a forthcoming publication [45]. As in most common water models, there was no Lennard-Jones inteaction center on the hydrogen atoms of silanol groups. Also, the Lennard-Jones parameter for silicon atoms was not optimized because probe molecules tended not to approach close to silicon atoms.

3 BINDING OF TRIPEPTIDES AT THE SILICA/WATER INTERFACE

Our studies of two tripeptides, lysine-tryptophan-lysine (KWK) and glutamic acid-tryptophan-glutamic acid (EWE)

(Figs. 2,3) were motivated by recent experiments by Brennan and co-workers probing the binding and fluorescence anisotropy of these tripeptides bound to Ludox silica nanoparticles [18, 46]. These workers observed strong binding of KWK, and weak binding of EWE to the silica nanoparticles [18]. They attributed binding exclusively to electrostatic interactions, based on their observations that KWK and acetylated KWK (Ac-KWK), the peptides with the most cationic amino groups, are the most strongly bound. They also cite disruption of KWK binding with increased salt as evidence of the primacy of electrostatic interactions [46].

A total of seven binding cases, four for KWK and three for EWE, were simulated in the ground state. Representative snapshots of peptides binding to the surface when the binding occurs through lysine or glutamic acid side or terminal groups are shown in Fig. 2. Two to four points of attachment between the tripeptides and the silica surface are typical for both KWK and EWE, and these attachments may arise between a variety of groups. For example, salt bridges between the amino acid groups of lysine side chains and dissociated silanol groups on the surface (Fig. 2a) is but one of many binding configurations observed for KWK. It is significant that in each trajectory we generated, the negatively charged EWE peptide stayed attached at the surface for the length of the runs of typical length of more than $20ns$. This explains how negatively charged species like albumin or DNA bind to the negatively charged silica surface.

There is an additional binding mechanism, shown in Fig. 3, in which the indole side group of the tryptophan finds a patch of the silica surface which, from random variations, is deficient in silanol groups. We have shown in previous publications [47–49] that regions of the surface with few silanols are hydrophobic, as evidenced by reduced density of water near these regions. In this regard, it is interesting to note that hydrophobic interactions have been proposed as an explanation for the stronger binding of single-stranded DNA to silica compared with double-stranded DNA [14, 16]. We also found that anionic carboxylic acid groups participate in binding to the silica surface. Very recently, Zhao *et al.* [27] performed *ab initio* self-consistent charge density functional tight-binding simulations of zwitterionic glycine near a periodic edingtonite surface and found that the carboxylic acid site strongly bound to the geminal silanol groups on this surface.

4 FURTHER STUDIES

Finally, we report initial binding studies of both single- and double-stranded DNA oligomers to the silica surface, which are in progress. A representative configuration is shown in Fig. In addition, simulation of the KWK and EWE tripeptides using a model for the excited state [50,51] are in progress, providing an interpretation for experimental fluorescence depolarization experiments [18, 46].

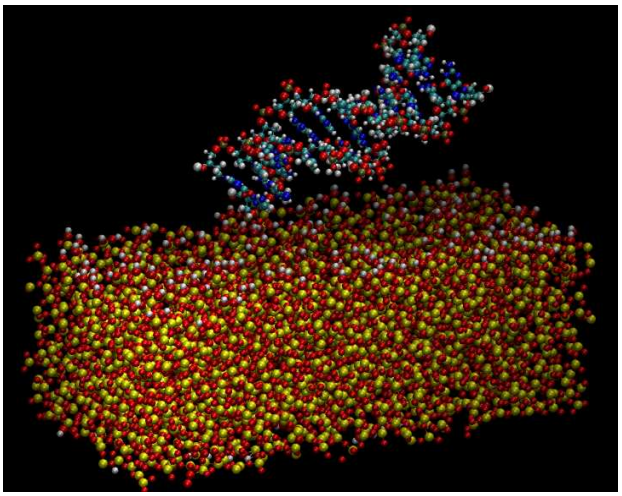

Figure 4: Snapshot of the Drew-Dickerson dodecamer (CGCGAATTCGCG) near a silica surface. Water and ions are not shown.

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REFERENCES

[1] R. K. Iler, *The Chemistry of Silica* (Wiley, New York, 1979).
[2] A. P. Legrand, ed., *The Surface Properties of Silicas* (Wiley, New York, 1998).
[3] N. C. Cady, S. Stelick, C. A. Batt, *Biosens. Bioelectron.* **19**, 59 (2003).
[4] I. Rech, *et al.*, *Electrophoresis* **27**, 3797 (2006).
[5] W. Schaertl, *Nanoscale* **2**, 829 (2010).
[6] W. J. M. Mulder, *et al.*, *Acc. Chem. Res.* **42**, 904 (2009).
[7] W. H. De Jong, P. J. A. Borm, *Int. J. Nanomed.* **3**, 133 (2008).
[8] Z. P. Xu, Q. H. Zeng, G. Q. Lu, A. B. Yu, *Chem. Eng. Sci.* **61**, 1027 (2006).
[9] X. Liang, K. J. Morton, R. H. Austin, S. Y. Chou, *Nano Lett.* **7**, 3774 (2007).
[10] B. Zhang, M. Wood, H. Lee, *Anal. Chem.* **81**, 5541 (2009).
[11] K. A. Melzak, C. S. Sherwood, R. F. B. Turner, C. A. Haynes, *J. Colloid Interface Sci.* **181**, 635 (1996).
[12] P. Mercier, R. Savoie, *Biospectroscopy* **3**, 299 (1997).
[13] M. Fujiwara, F. Yamamoto, K. Okamoto, K. Shiokawa, R. Nomura, *Anal. Chem.* **77**, 8138 (2005).
[14] S. H. Kang, M. R. Shortreed, E. S. Yeung, *Anal. Chem.* **73**, 1091 (2001).
[15] H.-W. Li, H.-Y. Park, M. D. Porter, E. S. Yeung, *Anal. Chem.* **77**, 3256 (2005).

[16] S. Isailovic, H.-W. Li, E. S. Yeung, *J. Chromatogr.* **A1150**, 259 (2007).
[17] S. R. Walter, F. M. Geiger, *J. Phys. Chem. Lett.* **1**, 9 (2010).
[18] J. Sui, D. Tleugabulova, J. D. Brennan, *Langmuir* **21**, 4996 (2005).
[19] M. Lundqvist, *et al.*, *Langmuir* **21**, 11903 (2005).
[20] J. J. Valle-Delgado, *et al.*, *Langmuir* **21**, 9544 (2005).
[21] M. van der Veen, W. Norde, M. C. Stuart, *Colloids Surf.* **B35**, 33 (2004).
[22] M. Nonella, S. Seeger, *ChemPhysChem* **9**, 414 (2008).
[23] H. Stutz, *Electrophoresis* **30**, 2032 (2009).
[24] A. Rimola, M. Sodupe, S. Tosoni, B. Civalleri, P. Ugliengo, *Langmuir* **22**, 6593 (2006).
[25] A. Rimola, B. Civalleri, P. Ugliengo, *Langmuir* **24**, 14027 (2008).
[26] A. Rimola, M. Sodupe, P. Ugliengo, *J. Phys. Chem.* **C113**, 5741 (2009).
[27] Y. L. Zhao, S. Köppen, T. Frauenheim, *J. Phys. Chem.* **C115**, 9615 (2011).
[28] J. Dabrowski, H.-J. Müssig, *Silicon Surfaces and Formation of Interfaces: Basic Science in the Industrial World* (World Scientific, River Edge, NJ, 2000).
[29] S. Yao, A. M. Myers, J. D. Posner, K. A. Rose, J. G. Santiago, *J. Microelectromech. Syst.* **15**, 717 (2006).
[30] B. Fubini, *The Surface Properties of Silicas*, A. P. Legrand, ed. (Wiley, New York, 1998), pp. 415–464.
[31] U. Saffiotti, *Acta Bio-Med. Ateneo Parmense* **76**, 30 (2005).
[32] W. R. Bowen, N. Hilal, R. W. Lovitt, C. J. Wright, *J. Colloid Interface Sci.* **197**, 348 (1998).
[33] K. Rezwan, L. P. Meier, L. J. Gauckler, *Biomaterials* **26**, 4351 (2005).
[34] S. J. McClellan, E. I. Franses, *Langmuir* **21**, 10148 (2005).
[35] P. Towner, *Essential Molecular Biology*, T. A. Brown, ed. (Oxford, London, 2000), vol. 1, chap. 3, pp. 55–67.
[36] O. Z. Nanassy, P. V. Haydock, M. W. Reed, *Anal. Biochem.* **365**, 240 (2007).
[37] P. M. Wolny, J. P. Spatz, R. P. Richter, *Langmuir* **26**, 1029 (2010).
[38] M. P. Allen, D. J. Tildesley, *Computer Simulation of Liquids* (Clarendon Press, New York, 1987).
[39] M. J. Frisch, *et al.*, Gaussian 03, Revision C.02. Gaussian, Inc., Wallingford, CT, 2004.
[40] C. Møller, M. Plesset, *Phys. Rev.* **46**, 618 (1934).
[41] R. J. Bartlett, D. M. Silver, *Int. J. Quantum Chem., Symp.* **8**, 271 (1974).
[42] R. J. Bartlett, D. M. Silver, *Int. J. Quantum Chem., Symp.* **9**, 183 (1975).
[43] J. S. Binkley, J. A. Pople, *Int. J. Quantum Chem.* **9**, 229 (1975).
[44] R. J. Bartlett, D. M. Silver, *Int. J. Quantum Chem.* **10**, 185 (1976).
[45] Y. K. Shin, A. A. Hassanali, S. J. Singer, Biomolecules at the amorphous silica/water interface: model development and application to binding and fluorescence anisotropy of peptides (2012). (submitted).
[46] D. Tleugabulova, J. D. Brennan, *Langmuir* **22**, 1852 (2006).
[47] A. A. Hassanali, S. J. Singer, *J. Phys. Chem.* **B111**, 11181 (2007).
[48] A. A. Hassanali, H. Zhang, C. Knight, Y. K. Shin, S. J. Singer, *J. Chem. Theory Comput.* **6**, 3456 (2010).
[49] H. Zhang, A. A. Hassanali, Y. K. Shin, C. Knight, S. J. Singer, *J. Chem. Phys.* **134**, 024705 (2011).
[50] A. A. Hassanali, T. Li, D. Zhong, S. J. Singer, *J. Phys. Chem.* **B110**, 10497 (2006).
[51] T. Li, A. A. Hassanali, S. J. Singer, *J. Phys. Chem.* **112**, 16121 (2008).