Exploring the properties of small molecule protein binding via molecular simulations: the TRSH-p53 core domain complex

Supplementary material: Assignment of quantum–mechanically derived partial charges

During the initial state of this study an assignment of *ab initio* generated partial charges via the well known "RESP" (restrained electrostatic potential) framework[1,2] was attempted. Due to the size of the molecule the application of a correlated *ab initio* treatment employing Møller-Plesset second–order perturbation theory (MP2) at the 6-31G(d,p) level[3,4] was achievable. To avoid possible errors from an artificial *in vacuo* treatment, the hydration was implicitly treated via a polarisable continuum model (PCM).[5] The calculation was carried out employing the software package Gaussian09.[6]

Partial charges for all atoms have been obtained via an electrostatic surface potential (ESP) fit. As the TRSH ion is a charged species, special focus has been given to the reproduction of the quantum–mechanically derived dipole moment, which was employed as a constrained in the fitting. Test calculations employing different density functionals and basis sets (*i.e.* 6-31G(d)[4]) as well as fitting without dipole constraint and/or PCM resulted only in minor numerical changes, whereas the overall trend in the distribution of the partial charges was retained. The largest deviation in these test calculations was observed at the Hartree-Fock level, which can be attributed to the inaccurate treatment of the correlation of electrons in this approach. The resulting ESP charges are listed in table S-1. As aliphatic CH_2 groups are represented via a united atom center in the GROMOS
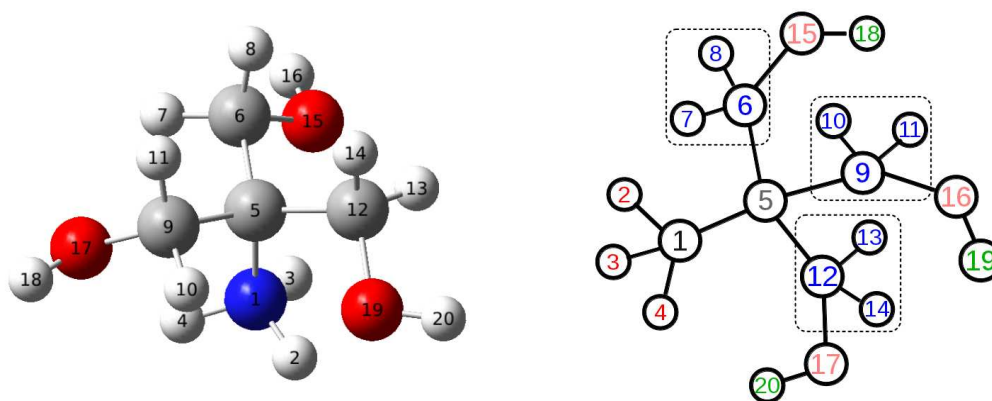

Figure S-1: Left: Optimised geometry of the TRSH residue at the MP2/6-31G(d,p)/PCM level depicting the atomic indices. Right: The coloring of the indices represents the six chemically equivalent species (black, red, grey, blue, orange, green). The CH_2 groups are represented via a united atom center.

force field, the hydrogen charges are added to the charge of the respective carbon atom. To obtain an equivalent assignment, the partial charges of chemically equivalent species have been averaged (see fig. S-1). Finally, the charges had to be slightly modified so that the GROMOS charge groups (see fig. S-2) appear neutral (hydroxymethyl groups) or with a net charge of $+1.0$ a.u (ammonium group plus quaternary carbon atom).

Irrespective of the established use of ESP derived charges in some force–field approaches, the application of the quantum mechanically derived charges in MD simulations of the TRSH-p53 system proved unsuccessful. This is due to the fact, that the partial charges of the GROMOS force fields have not been derived on the basis of quantum–chemical computations and hence, such an approach proved unsuitable in our investigation, as the compatibility of the ligand-, protein- and solvent-parameters was not ensured. In order to derive more suitable partial charges for the TRSH residue, building blocks of other species defined in the GROMOS force fields[7,8] have been employed as template as outlined in the main manuscript.

Table S-2 presents a comparison of the partial charges for TRSH residue employing the amino–terminal and serine side–chain charge groups of the GROMOS 45A4 and 53A6 force fields with the quantum–mechanically derived charges. It can be seen that the ESP charges are more polarised in case of the hydroxy groups and even more in the vicinity of the nitrogen atom. If the charge distribution of all residues of the force field are derived with the same procedure, such effects would not cause any difficulties, provided that the remaining force–field parameters are adequate as well. However, since the TRSH residue was the only species parametrised via an ESP calculation in the aforementioned tests, an incompatibility with the GROMOS force field arose, which was not the case when a charge assignment based on the amino–terminal and serine side–chain charge group was employed.
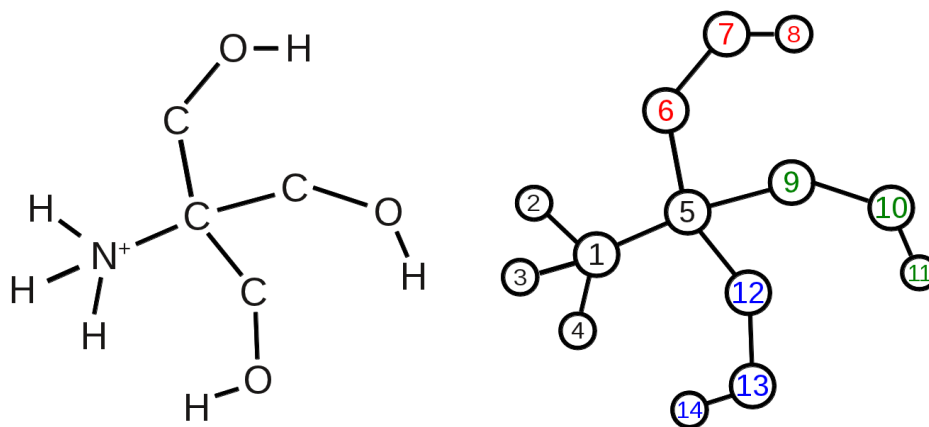

Figure S-2: Left: Topology of the TRSH residue in the GROMOS force field. The CH_2 groups are represented via a united atom center. Right: The coloring of the indices represents the four charge groups (black, red, green, blue).

References

[1] C. Bayly, P. Cieplak, W. Cornell, P. Kollman, *J Phys Chem* **1993**, *97*, 10269.

[2] W. Cornell, P. Cieplak, C. Bayly, P. Kollman, *J Am Chem Soc* **1993**, *115*, 9620.

[3] W. J. Hehre, R. Dithfield, J. A. Pople, *J Chem Phys* **1972**, *56*, 2257.

[4] P. C. Hariharan, J. A. Pople, *Theor Chim Acta* **1973**, *28*, 213.

[5] G. Scalmani, M. J. Frisch, *J Chem Phys* **2010**, *132*, 114110.

[6] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, . Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox. Gaussian 09. Gaussian Inc. Wallingford CT 2009.

[7] L. D. Schuler, X. Daura, W. F. van Gunsteren, *J Comput Chem* **2001**, *22*, 1205.

[8] C. Oostenbrink, A. Villa, A. E. Mark, W. F. van Gunsteren, *J Comput Chem* **2004**, *25*, 1656.

	Atom	ESP charge	UA-charge	average	MM charge
1	N	-0.355			-0.360
2	H	0.321			
3	H	0.317		0.319	0.320
4	H	0.319			
5	C	0.400			0.400
6	C	0.052			
7	H	0.081	0.194		
8	H	0.061			
9	C	0.009			
10	H	0.095	0.179	0.189	0.190
11	H	0.074			
12	C	0.044			
13	H	0.083	0.193		
14	H	0.065			
15	O	-0.663			
16	O	-0.667		-0.667	-0.670
17	O	-0.673			
10	H	0.475			
15	H	0.480		0.478	0.480
20	H	0.479			

Table S-1: Atomic partial charges of the TRSH molecule obtained from an ESP fit at MP2/6-31G(d,p)/PCM level, resulting partial charges of united atom (UA) groups, average over chemically equivalent atoms/groups and MM charges derived for the individual charge groups for the application in simulation studies employing the GROMOS force field. (charges are given in atomic units)

		45A4	53A6	ESP
1	N	0.129	0.129	-0.360
2	H	0.248	0.248	0.320
3	H	0.248	0.248	0.320
4	H	0.248	0.248	0.320
5	C	0.127	0.127	0.400
6	C	0.150	0.266	0.180
7	O	-0.548	-0.674	-0.660
8	H	0.398	0.408	0.480
9	C	0.150	0.266	0.180
10	O	-0.548	-0.674	-0.660
11	H	0.398	0.408	0.480
12	C	0.150	0.266	0.180
13	O	-0.548	-0.674	-0.660
14	H	0.398	0.408	0.480

Table S-2: Comparison of partial charges derived for the TRSH molecule employing the amino-terminal and serine side–chain charge groups of the GROMOS 45A4 and 53A6 force fields and the ESP charges. Due the large difference the latter charges proved not compatible to either of the two GROMOS force fields in trial simulations. (charges are given in atomic units)