Supplementary Material for PCCP

Electronic Supplementary Information

Theoretical Analysis of Intermolecular Interactions of Selected Residues of Triosephosphate Isomerase from *Trypanosoma cruzi* with its Inhibitor 3-(2-Benzothiazolylthio)-1-propanesulfonic Acid

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1 MP2/CBS dissociation profiles for selected BTT-amino acid complexes

The use of the MP2 aproximation with a small basis set is known to reproduce interaction energies for weakly bonded complexes with fairly good accuracy, when corrected for the BSSE. However, it is always a good practice to compare the results obtained in this fashion with higher-level calculations whenever they are computationally allowable. In the case of the BTT-aminoacid complexes studied in the accompanying paper, the extrapolation of the MP2 energies to the complete basis set limit (MP2/CBS) was performed as a benchmark. As shown in Table S-1, the MP2/CBS results are very similar to those obtained at the MP2/6-31++G** level. For a qualitative comparison, Figure S-1 shows the dissociation curves for the complexes of BTT with phe75A, tyr102B and arg71A obtained with the two methods which give the same description within chemical accuracy. However, the non-extrapolated approach is preferred in our work because it provides, besides the energetics of the molecular association, a description of the electron density that can be used for further analysis.

Table S-1: Interaction energies (in kcal/mol) obtained with the BSSE-corrected MP2/6-31++G** and the MP2/CBS methods for selected BTT-amino acid complexes at the configuration observed in the X-ray structure (columns 2 and 4), and at the optimum distance for this orientation (columns 3 and 5). In parenthesis are shown the corresponding distances (in Å) between centers of mass for each case.

	MP2/6-31++G**		MP2/CBS	
Complex	E_{int}	E_{int}^{min}	E_{int}	E_{int}^{min}
BTT-phe75A	-2.734 (8.57)	-2.819 (8.42)	-3.009 (8.57)	-3.262(8.32)
BTT-arg71A	-1.188 (9.41)	-1.269 (9.54)	-1.627 (9.41)	-1.629(9.42)
BTT-tyr102B	+3.136 (7.24)	-0.538 (8.08)	2.144 (7.24)	-0.730(7.95)

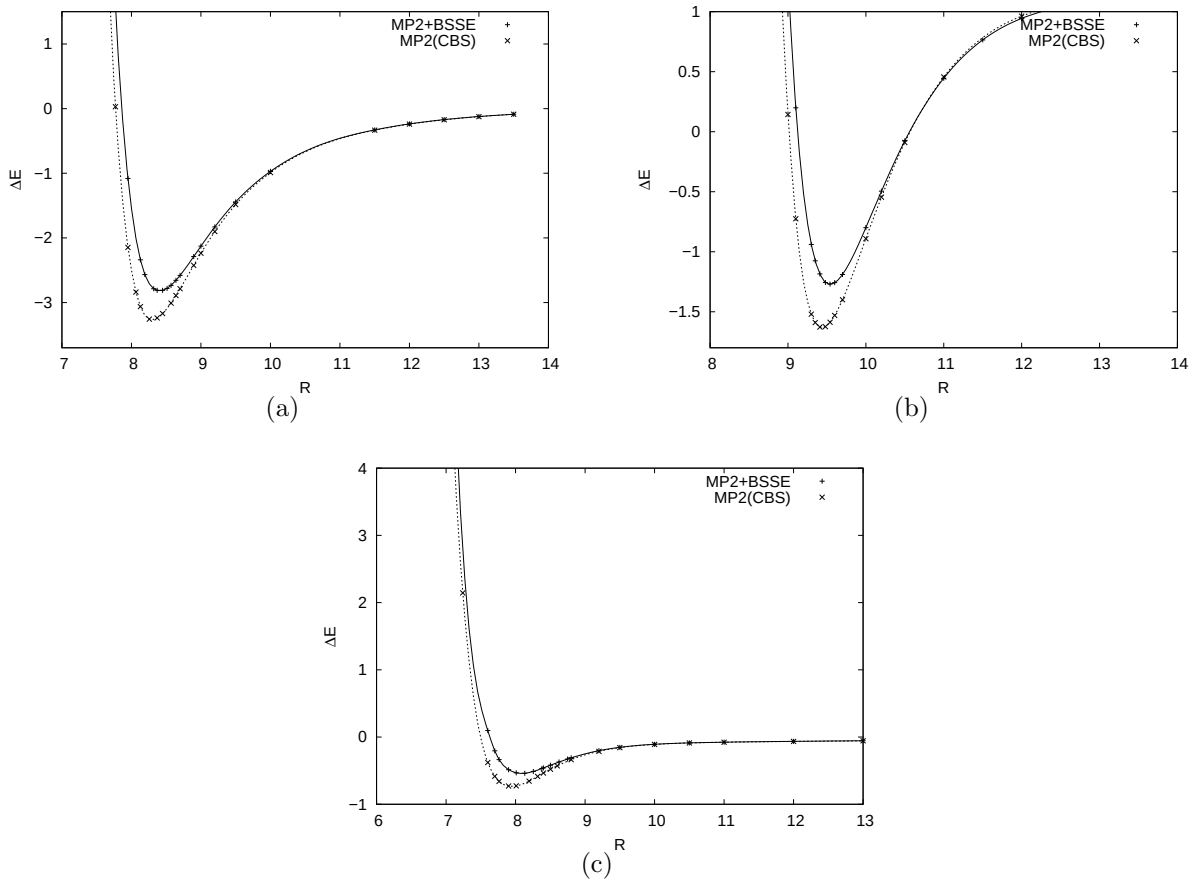


Figure S-1: Dissociation profiles for the complexes of BTT with (a) phe75A, (b) arg71A and (c) tyr102B obtained with the BSSE-corrected MP2/6-31++G** and the MP2/CBS methods. Energies in kcal/mol, and distances in Å. Further details are provided in accompanying paper.

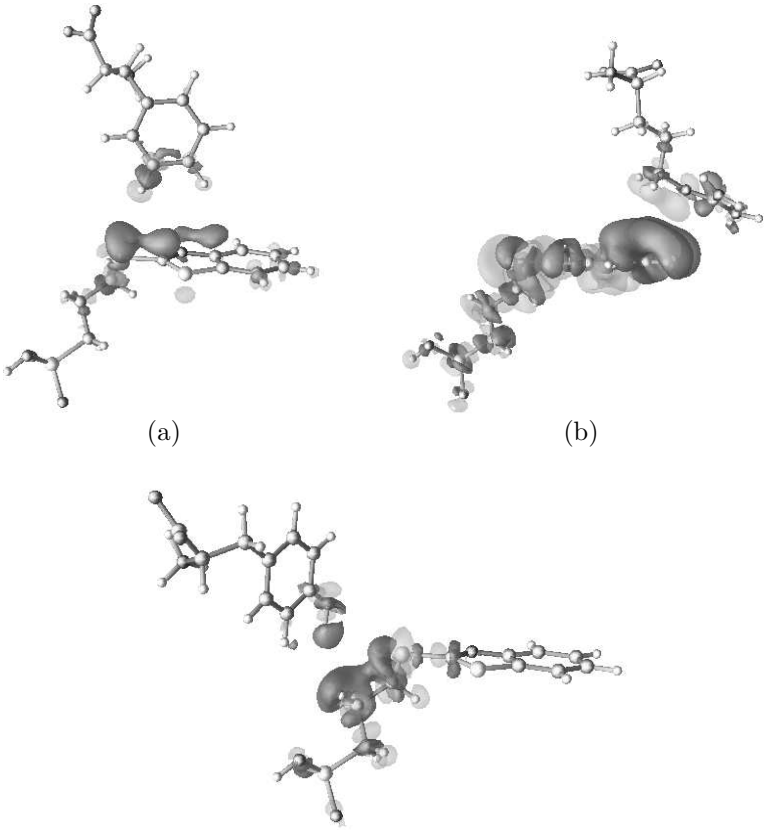
2 Interaction densities for selected BTT-amino acid complexes

The sign of the interaction density $\rho^{int}(\mathbf{r})$ at an intermolecular bond critical point, ρ_b^{int}, was not found to reflect the energetic nature of the interactions (whether stabilizing or not) in the complexes under study. For these weakly bonded systems, the charge redistribution at the bond critical points, *bcps*, is small ($\sim 10^{-5}$ a.u.) and almost negligible compared to the value of the electron density at the same point, ρ_b. However, it is interesting to note (Table S-2) that the biggest positive value of ρ_b^{int}/ρ_b observed for the intermolecular *bcps* of the complexes under study corresponds to the BTT-phe75A pair, the energetically most favourable one. In the same fashion, the biggest negative values (charge depletion relative to the isolated moieties) of ρ_b^{int}/ρ_b for the same set are those of the BTT-tyr102B complex, the only one with a repulsive interaction. Whether or not this trend persists for other systems is yet a conjecture to be explored.

Table S-2: Electron density and percentual electron density change due to complexation at the intermolecular *bcps* for the BTT-amino acid complexes studied.

Complex	Atoms X,Y	ρ_b	% (ρ_b^{int}/ρ_b)
BTT-phe75A	S,H	0.005	+0.46
	C,H	0.003	+2.21
BTT-arg71A	C,N	0.007	-0.57
BTT-tyr102B	H,O	0.014	-2.89
	H,H	0.012	-2.28

To complete the discussion, Figure S-2 shows representative isosurfaces of $\rho^{int}(\mathbf{r})$ maps for the complexes of BTT with each of the aminoacids forming its recognition site in the TcTIM enzime (phe75A, arg71A and tyr102B), at the minimum of the corresponding MP2/6-31++G** disociation profile of Figure S-1 (column 3 in Table S-1). Note that, relative to their size at the crystal structure configuration (Figure 5 in the paper), the envelopes of $\rho^{int} = \pm 0.0004$ have shrinked for the BTT-tyr102B complex, and expanded for the BTT-phe75A pair, bringing them to a comparable size. For the BTT-arg71A complex, the same pattern of strong charge polarization along the whole BTT molecule is observed as a result of its association with the cationic side-chain of the arg71A fragment.



(a) (b)

(c)

Figure S-2: Isosurfaces (± 0.0004) of $\rho^{int}(\mathbf{r})$ for the complexes of BTT with a) phe75A, b) arg71A and c) tyr102B at the minimum of the corresponding dissociation profile. Positive and negative values are shown in dark and light shading respectively.