J Incl Phenom Macrocycl Chem (2007) 57:375–377
DOI 10.1007/s10847-006-9257-0

ORIGINAL ARTICLE

Comparison of estimates of free energy for binding of mono- and di-substituted benzenes with α-cyclodextrin obtained by single-step perturbation and thermodynamic integration

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Received: 15 May 2006 / Accepted: 20 October 2006 / Published online: 30 January 2007

Abstract In this work, the relative free energies of binding individual members of a series of mono- and di-substituted benzenes to α-cyclodextrin in water have been estimated using the single step perturbation methodology (SSP). The computations involved were based on 5 ns molecular dynamics simulations of a judiciously chosen unphysical reference state and its complex with α-CD in water. The thermodynamic integration method (TI) was also used to calculate the relative free energies of binding for comparison purposes. The results of SSP computations were in good agreement with experimental data. The results also show that the SSP technique exhibits a potential alternative to more traditional but more expensive free energy computational methods.

Keywords Substituted benzenes · α-Cyclodextrin · Single step perturbation · Thermodynamic integration

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Introduction

The single step perturbation (SSP) method provides a convenient technique to estimate free energies of binding of a series of closely related compounds to a common receptor. This is carried out by using a judiciously chosen unphysical reference state [1, 2], which avoids the time-consuming simulation of intermediate states required by traditional free energy perturbation (FEP) and thermodynamic integration (TI) methods. Thus SSP seems to provide a reasonable alternative especially when estimates of free energies of binding for a series of compounds to a common receptor are needed.

In this work, the SSP approach was used to calculate the relative free energies of binding a series of mono- and di-substituted benzenes to α-cyclodextrin (α-CD) in water. The TI technique was also used to calculate relative free energies of binding for comparison purposes.

Compuational methods

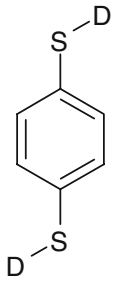
All simulations were performed using the GROMOS simulation software package [3]. Interaction parameters were taken from the 53A5 GROMOS parameter set [4]. Molecular dynamics simulations of the interacting molecules were conducted in water at $T = 298\ K$ and $P = 1$ atm using explicit SPC water.

The relative free energies of binding using the TI method were calculated as follows:

$$\Delta G_{AB} = \int_{\lambda_A}^{\lambda_B} \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} d\lambda \qquad (1)$$

where V is the potential energy and λ is a coupling parameter. A total of 21 lambdas were used; for each lambda a 300 ps was used for equilibration and 500 ps for sampling.

For SSP calculations, two 5 ns long MD simulations were conducted, one for the unphysical reference guest (R) in water and one for R bound to α-cyclodextrin in water. The reference guest is the disubstituted benzene shown below



where D stands for dummy atoms and S for soft atoms for which the nonbonded interaction functions have been modified to remove the singularity at the origin. This may be obtained by writing the Lennard–Jones interaction for atom i and j with Cartesian coordinates $\boldsymbol{r_i}$ and $\boldsymbol{r_j}$ as follows [1]:

$$E^{\mathrm{vdw}}(r_{ij}) = \left(\frac{\mathrm{C}_{12}}{\alpha + r_{ij}^6} - \mathrm{C}_6\right)\frac{1}{\alpha + r_{ij}^6} \tag{2}$$

where α is a small offset to the distance between the atoms, while C_6 and C_{12} are the van der Waals interaction parameters of the force fields for the particular pair of atoms. The force field parameters for the soft atom were the same as for the Br atom in the 53A5 GROMOS parameter set. The value for α used was set to $0.3775 \times C_{12}/C_6$.

Results and discussion

The SSP relative free energy of binding for two different compounds, B and A, can be obtained from a thermodynamic cycle (Fig. 1) by taking the difference of the relative free energies ($\Delta\Delta G_{\mathrm{BA}}$) of changing the reference compound into compounds B and A in their free and complexed states in water according to:

$$\Delta\Delta G_{\mathrm{BA}} = \Delta G_{\mathrm{B}} - \Delta G_{\mathrm{A}} = (\Delta G_{\mathrm{BR}}^{\mathrm{complex}} - \Delta G_{\mathrm{BR}}^{\mathrm{free}}) - (\Delta G_{\mathrm{AR}}^{\mathrm{complex}} - \Delta G_{\mathrm{AR}}^{\mathrm{free}}) \tag{3}$$

The free-energy difference between a reference state (R) and a real physical state A can be calculated from a simulation of state R using the perturbation formula:

$$\Delta G_{\mathrm{AR}} = -k_{\mathrm{B}} T \ln\langle \mathrm{e}^{-(E_{\mathrm{A}} - E_{\mathrm{R}})/k_{\mathrm{B}}T}\rangle_{\mathrm{R}} \tag{4}$$

where the brackets indicate an ensemble average over the structures generated in a simulation of R, E_{A} and E_{R} are the potential energies for the physical state (A) and the reference state (R), respectively, k_{B} is the Boltzmann constant, and T is the absolute temperature.

For each system, there are two possible approaches for the substituent to α-CD since it may be located near the narrow rim or wide rim of α-CD. Thus, a combined result for the two main binding orientations was obtained by including them into the ensemble average of Eq. (4).

The values of the relative binding energies of mono- and di-substituted benzenes to α-CD, with respect to benzene, are given in Table 1.

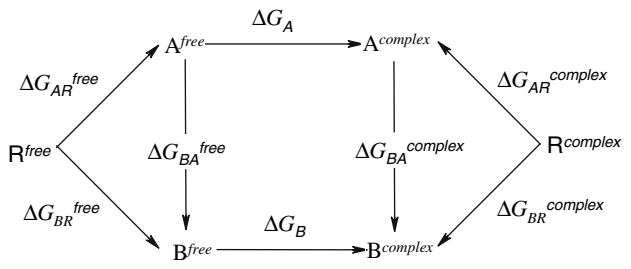


Fig. 1 The thermodynamic cycle used to calculate the relative free energies

Table 1 The results of the SSP and TI calculations

Substituents		$\Delta\Delta G_{\mathrm{binding}}$ (kJ/mol)		
X	Y	SSP	TI	Expt [5, 6]
H	F	–1.3	–4.6	–0.8
H	Cl	–6.1	–6.1	–3.4
H	Br	–9.7	–7.8	–7.3
F	F	–4.3	–	1.0
F	Br	–7.5	–	–5.4
F	Cl	–4.6	–	–2.0
Cl	Br	–13.5	–	–
Cl	Cl	–10.7	–6.2	–5.1
Br	Br	–16.8	–8.7	–8.9
F	CH_3	–3.4	–	–
OH	F	–7.8	–	–0.7
Cl	CH_3	–10.7	–	–
OH	Cl	–10.4	–6.1	–5.8
CH_3	Br	–13.5	–	–
OH	Br	–13.3	–6.8	–8.0
CH_3	CH_3	–10.6	–5.8	–2.3
OH	OH	–4.3	–3.2	–
CH_3	H	–5.9	–4.1	–0.6
OH	H	–2.6	–3.6	–0.6
OH	CH_3	–8.0	–6.6	–1.4

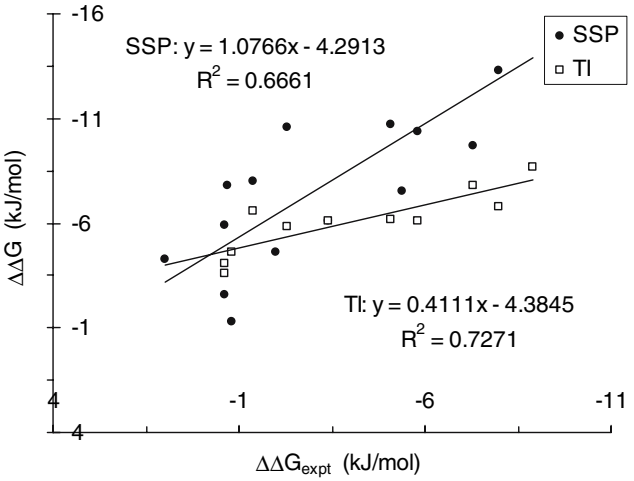


Fig. 2 A plot of $\Delta\Delta G_{\text{binding}}$ obtained by SSP and TI against experimental values

The results obtained using TI and experimental data are also shown. Figure 2 depicts a plot of the relative binding energies obtained from the SSP and TI methods against experimental data. Keeping in mind the inherent errors associated with free energies obtained from experimentally determined complex formation constants ($\Delta G_{\text{exp}} = -RT \ln K_{\text{exp}}$), and the apparent difference in the R^2 values depicted in Fig. 2 (0.666 and 0.727), it is clear that the slope of SSP vs experimental free energies is almost unity (1.077) compared with 0.411 for TI against experimental free energies. It should be emphasized, however, that both SSP and TI methods are offset from experimental data by –4.3 ± 0.1 kJ/mol. Evidently, the SSP method appear to correlate better with experimental data (slope ≈ 1) than the TI method (slope ≈ 0.4) for the two series of mono- and di-substituted benzenes. Moreover, the SSP method is computationally much less expensive since only two MD trajectories are needed to estimate the relative binding energies of several compounds. In contrast, TI methods require simulations of all possible mutations among all members of the series in the absence and presence of α-CD. This certainly makes the SSP approach a promising technique, especially in screening out the affinities of series of guest compounds to the same host. Future work would have to tackle the possible use of unphysical reference states involving a variable number of soft atoms. This would certainly allow exploration of the possible extension of the application of the SSP method to a series of compounds which are not necessarily homologous.

Conclusion

Single step perturbation (SSP) and thermodynamic integration (TI) methodologies were used to calculate the relative free energies of binding members of a series of mono- and di-substituted benzenes to α-cyclodextrin (α-CD) in water. The results indicate that the SSP method provides a promising approach which may compete with the TI method for the prediction of free energies of the complexes examined in this work. Moreover, the SSP method offers a relatively less expensive alternative technique for estimating relative free energy of binding series of closely related compounds to a common receptor such as cyclodextrin molecule.

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