S1

Validation of the Solvation Model

Throughout this work, stationary points were obtained by means of full (unconstrained) optimisation in solution using PCM/6-31+G*. Solvation was subsequently simulated by means of a single point correction to the SCF energy using COSMO/B3LYP/6-311+G**. In all cases, the reaction barrier was calculated as the difference between transition state energies relative to the sum energies of the phosphate diester and nucleophile (at infinite separation). This effectively involves taking the difference in solvation between a state with a high negative charge (TS, -2) and two states with lower negative charge (diester and nucleophile, both -1). Considering the charge difference between the species, it is important to see whether the continuum model is able to effectively screen charge-charge interactions, and reproduce consistent and accurate solvation energies. In order to validate this, we have selected two of our compounds (the parent and the 4-nitro compounds) and have examined the change in solvation upon modifying the oxygen Van der Waals radii (R) over a range of 2.0 to 1.0Å. This data is presented in Tables 1, and Figs. 1 and 2 show the change in $\Delta\Delta G_{solv}$ (i.e. the difference in solvation between the transition state and the moieties at infinite separation) upon changing R. In the case of the parent compound (Table 1 and Fig. 1), $\Delta\Delta G_{solv}$ changes by less than 1 kcal/mol. In the case of the 4-nitro substituted compound (Table 1 and Fig. 2), the change in $\Delta\Delta G_{solv}$ is more significant, and ideally, solvation should be simulated using R≈1.4Å, which gives the best solvation energy for OH⁻. However, in the range of R ~ 1.4 to 1.7 Å, even for the 4-nitro substituted compound, the change in $\Delta\Delta G_{solv}$ is less than 3 kcal/mol Apparently, while the COSMO results depend significantly on the atomic radii, and in some cases are not calibrated perfectly, the change in the solvation energy with distance is quite stable and reasonable. Thus, although the ideal approach for simulating solvation would be the use of a combined QM/MM free energy perturbation approach using explicit water

1

molecules (the methodology for which is currently being developed by us), these results demonstrate that our solvation model screens charges effectively and consistently, and is adequate and reliable for the systems being studied. This is further reinforced by the fact that for each compound studied, we have reproduced ΔG_{exp} with significant accuracy.

R	OH$^-$	Parent			4-nitro		
		Diester	TS	$\Delta\Delta G_{solv}$	Diester	TS	$\Delta\Delta G_{solv}$
Default	-92.16	-73.99	-221.02	**-54.87**	-66.45	-202.35	**-43.74**
2.0	-81.39	-65.40	-200.97	**-54.18**	-65.14	-219.13	**-39.55**
1.9	-85.08	-68.28	-208.04	**-54.68**	-65.76	-224.11	**-44.29**
1.8	-88.97	-71.32	-215.15	**-54.86**	-66.41	-226.07	**-47.20**
1.7	-92.98	-74.55	-222.94	**-55.41**	-67.04	-224.80	**-47.73**
1.6	-97.06	-77.61	-229.75	**-55.08**	-67.74	-221.44	**-47.85**
1.5	-100.94	-80.16	-236.59	**-55.39**	-68.46	-216.08	**-46.68**
1.4	-104.23	-82.57	-242.28	**-55.48**	-69.36	-209.77	**-44.97**
1.3	-106.67	-83.68	-245.95	**-55.60**	-70.40	-203.49	**-43.47**
1.2	-107.01	-83.17	--	--	-71.86	-195.88	**-40.50**
1.1	-104.46	-80.69	--	--	-75.36	-189.19	**-38.35**
1.0	-97.49	-76.33	--	--	-82.09	-182.93	**-36.40**

Table 1: Variation of the solvation energy with the oxygen Van der Waals radius (R) for the parent and 4-nitro substituted compounds. R is given in Å and all solvation energies are given in kcal/mol. In both cases, $\Delta\Delta G_{solv}$ denotes the difference in solvation between the transition state and the moieties at infinite separation. Missing values could not be obtained due to convergence problems at small values of R.
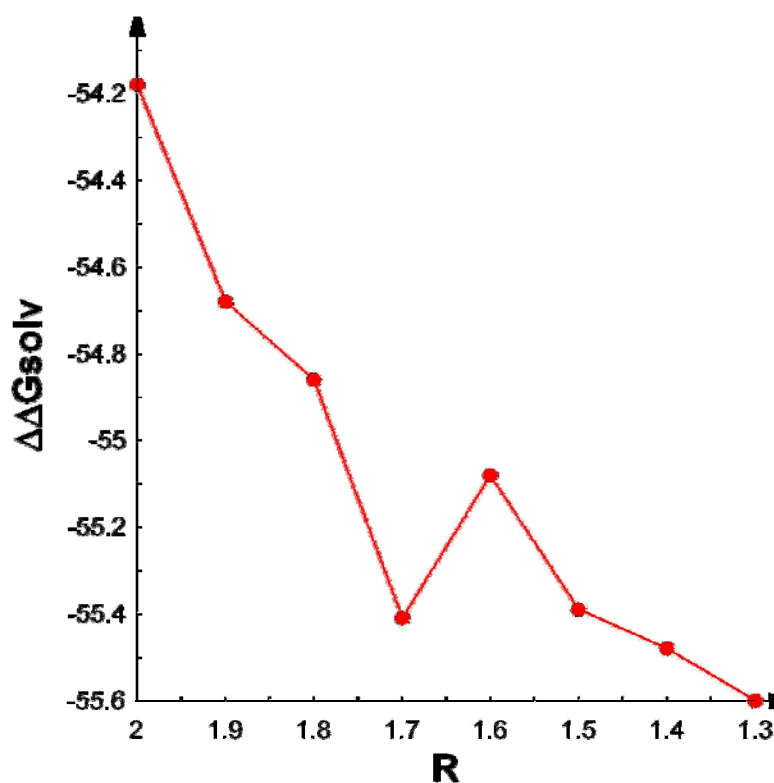
Figure 1: The effect of modifying the oxygen Van der Waals radii of the parent compound on solvation. $\Delta\Delta G_{solv}$ denotes the difference in solvation between the transition state and the moieties at infinite separation (in kcal/mol) and R denotes the oxygen radius (in Å).
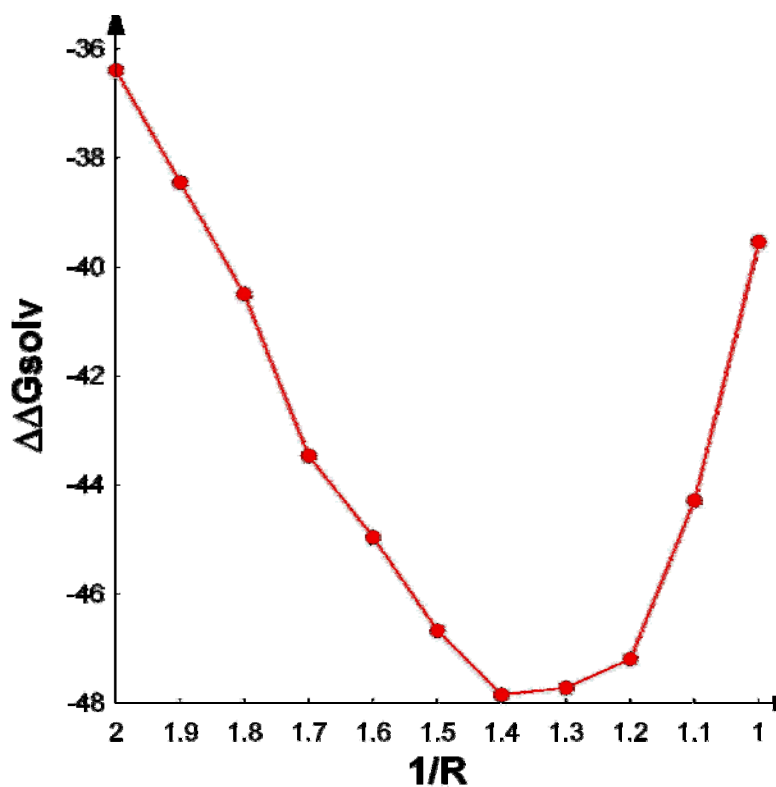

Figure 2: The effect of modifying the oxygen Van der Waals radii of the 4-nitro substituted compound on solvation. $\Delta\Delta G_{solv}$ denotes the difference in solvation between the transition state and the moieties at infinite separation (in kcal/mol) and R denotes the oxygen radius (in Å).