

1 Supplementary Information

Here we present technical details relevant to the arguments made in the main paper. Table 1 provides the information required to evaluate the accuracies of the energy of inserting a van der Waals cavity into solution (ΔG_{vdw}) and its repulsive (ΔG_{rep}) and attractive (ΔG_{att}) components. Figure 1 of this supplementary material shows the attractive and repulsive integrands for the λ -integrations for one of the decaalanine conformers. The smoothness of these plots combined with the data in Table 1 indicate that our estimates of ΔG_{rep} and ΔG_{att} were well converged. In Figure 2 we show ΔG_{rep} , ΔG_{att} , and linear response and perturbative estimates of ΔG_{att} for our systems plotted against the solvent-excluded surface area (A). Figure 3 shows ΔG_{vdw} as a function of A . Figure 4 shows ΔG_{rep} plotted against the solvent-excluded volume (V) for the alkanes, and Figure 5 shows ΔG_{vdw} plotted against V . Figure 6 shows the derivative ($\partial\Delta G_{\text{att}}/\partial x_i$) of ΔG_{att} with respect to the atomic positions (x_i) versus the derivative of A with respect to x_i for the decaalanines. Figure 7 shows the derivatives of ΔG_{rep} and ΔG_{att} with respect to the x_i versus the derivative of A with respect to the x_i . Figure 8 shows the derivative of ΔG_{vdw} with respect to x_i versus the derivative of V with respect to x_i .

Table 1: FEP estimates of ΔG_{rep} , ΔG_{att} , and ΔG_{vdw} .

Decaalanines						
Molecule	ΔG_{rep}		ΔG_{att}		ΔG_{vdw}	
	B	F	B/S	F/L	B+B/S	F+F/L
d	94.18	94.22	-71.10	-71.05	23.08	23.17
d1	79.23	79.49	-55.06	-54.91	24.18	24.58
d2	83.66	83.77	-59.82	-59.76	23.84	24.01
d3	90.42	90.47	-66.87	-67.10	23.55	23.37
Alkanes						
Methane	6.47	6.73	-4.23	-4.24	2.25	2.49
Ethane	9.60	9.33	-6.76	-6.76	2.85	2.57
Propane	11.42	11.64	-8.96	-8.97	2.46	2.67
Butane	14.11	14.10	-11.03	-11.02	3.08	3.08
Pentane	16.17	16.58	-13.03	-12.99	3.14	3.59
Hexane	18.67	18.52	-14.91	-14.97	3.76	3.55
Isobutane	13.54	13.82	-10.91	-10.87	2.63	2.95
2-Methylbutane	15.78	16.35	-12.72	-12.73	3.07	3.62
Neopentane	15.49	14.93	-12.59	-12.56	2.91	2.37
Cyclopentane	14.25	14.34	-12.38	-12.43	1.87	1.91
Cyclohexane	16.47	16.16	-14.18	-14.13	2.29	2.03

The numbers in the column labeled B were derived from backward FEP, those in the column labeled F were derived from forward FEP, those in the column labeled B/S were derived from backward FEP for the alkanes and from simulations that were half as long as the final simulations for the decaalanines, those in the column F/L were derived from forward FEP for both systems, and the columns labeled B+B/S and F+F/L were derived by adding the numbers in the appropriate columns.

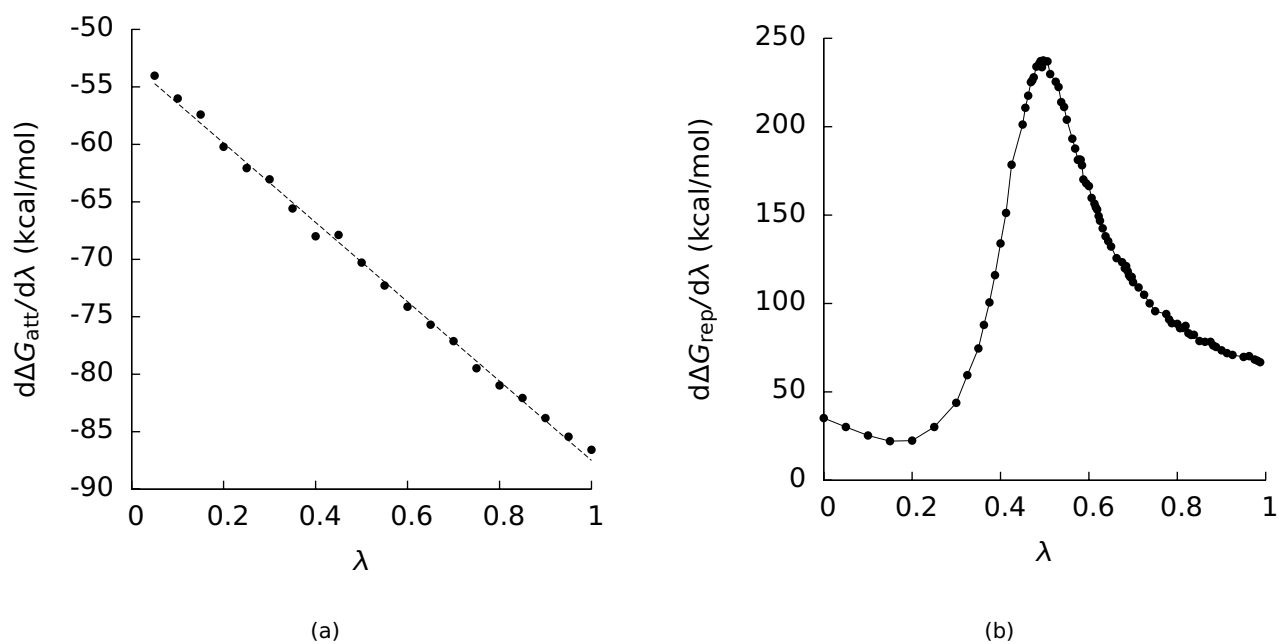


Figure 1: a) The derivative ($\partial\Delta G_{\text{att}}/\partial\lambda$) of the attractive component of the energy required to form a van der Waals cavity (ΔG_{vdw}) with respect to the integration coordinate (λ) as a function of λ for the decaalanine d. b) The derivative ($\partial\Delta G_{\text{rep}}/\partial\lambda$) of the repulsive component of ΔG_{vdw} with respect to λ as a function of λ for the decaalanine d.

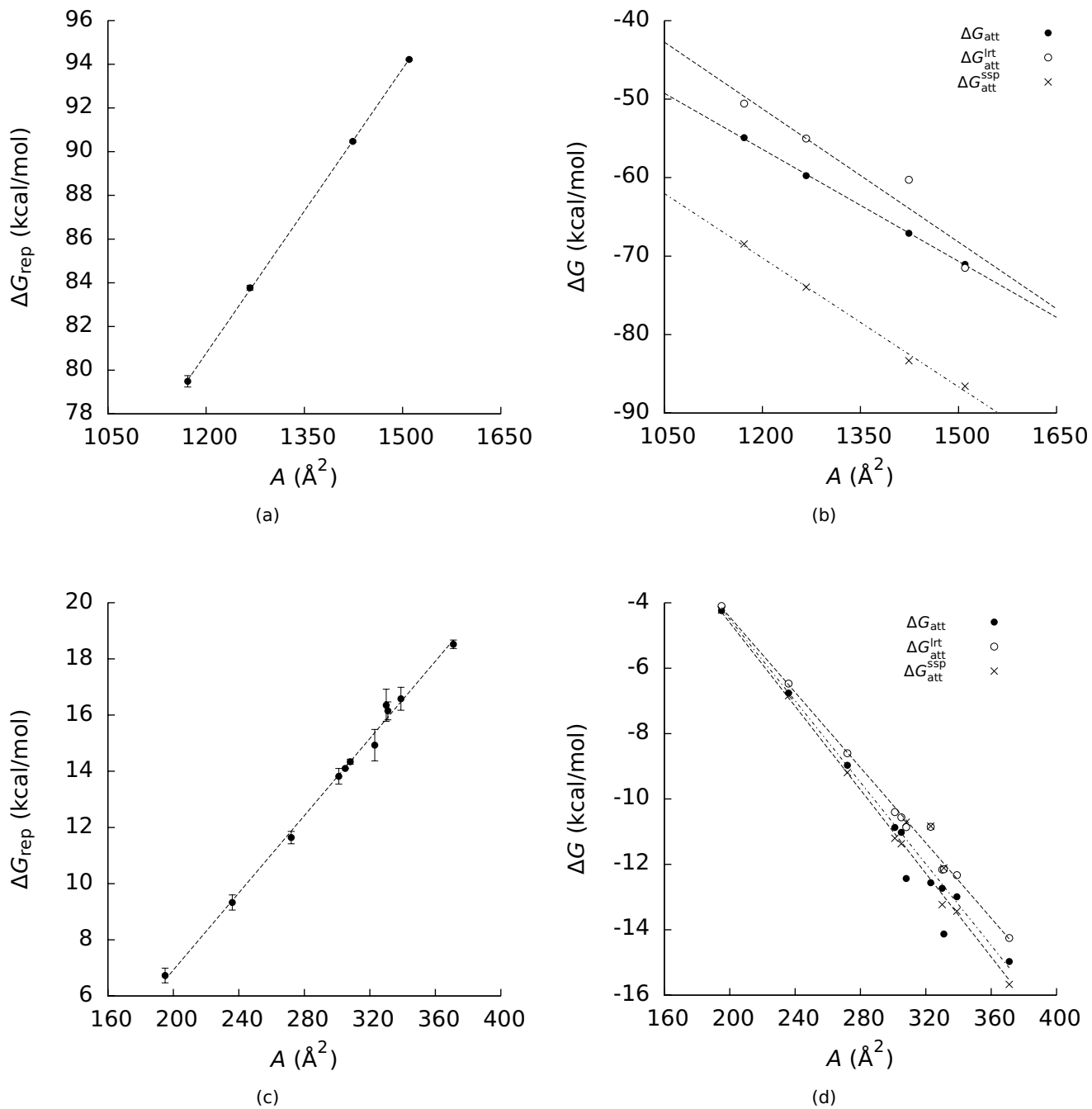


Figure 2: a) The repulsive component (ΔG_{rep}) of the energy required to form a van der Waals cavity (ΔG_{vdw}) as a function of the solvent-accessible surface area (A) for the decaalanine conformations. b) The attractive component (ΔG_{att}) of ΔG_{vdw} and the linear response ($\Delta G_{\text{att}}^{\text{lrt}}$) and single step perturbation ($\Delta G_{\text{att}}^{\text{ssp}}$) estimates of ΔG_{att} as functions of A for the decaalanine conformations. c) and d) show the same plots for the alkanes. The error bars in panels a) and c) are equal to the difference between the values obtained with forward free energy perturbation (FEP) and backward FEP. Similar error bars in panels b) and d) would be smaller than the data points.

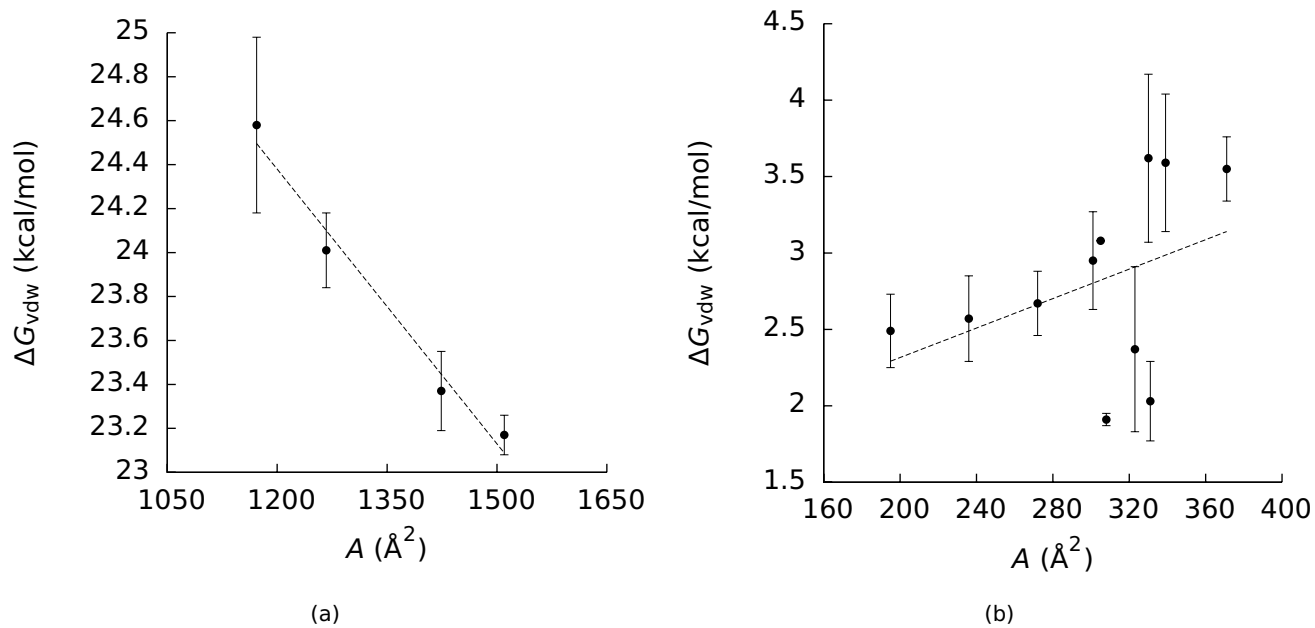


Figure 3: The energy required to form a van der Waals cavity (ΔG_{vdw}) as a function of the solvent-accessible surface area (A) for a) the decaalanine conformations and b) the alkanes. The error bars represent the difference between the columns labeled F+F/L and B+B/L in Table S1.

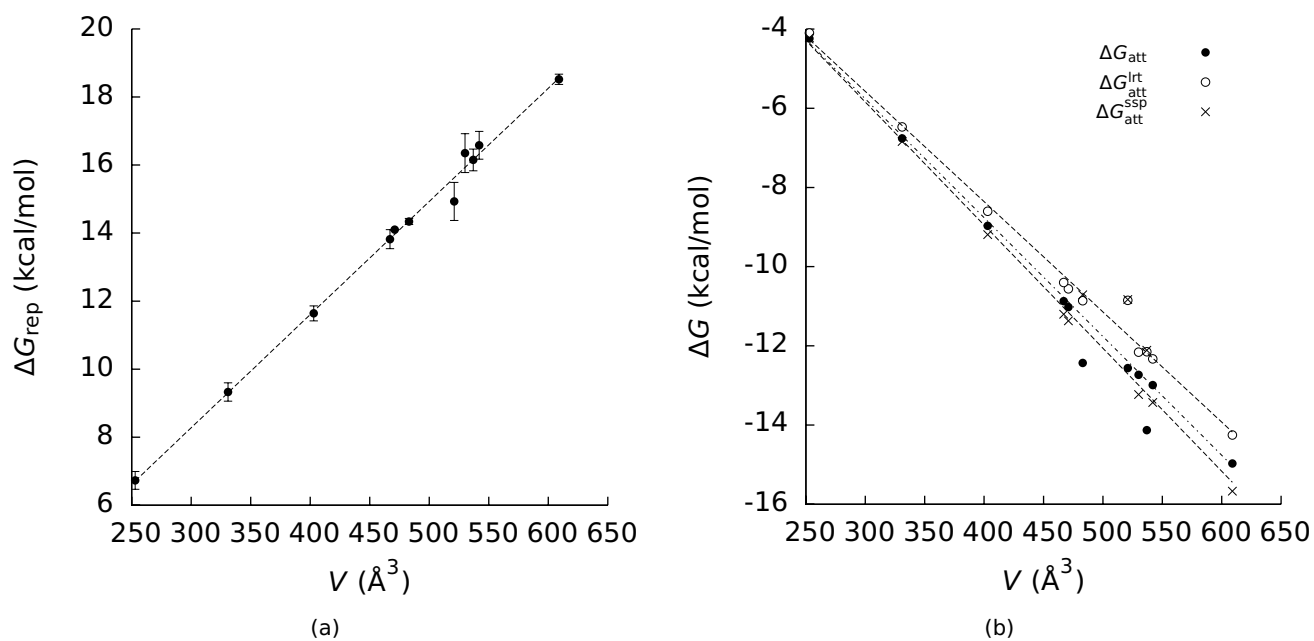


Figure 4: a) The repulsive component (ΔG_{rep}) of the energy required to form a van der Waals cavity (ΔG_{vdw}) as a function of the solvent-accessible volume (V) for the alkanes. b) The attractive component (ΔG_{att}) of ΔG_{vdw} and the linear response ($\Delta G_{\text{att}}^{\text{lrt}}$) and single step perturbation ($\Delta G_{\text{att}}^{\text{ssp}}$) estimates of ΔG_{att} as functions of V for the alkanes. The error bars in panel a) are equal to the difference between the values obtained from forward free energy perturbation (FEP) and backward FEP. Similar error bars in panel b) would be smaller than the data points.

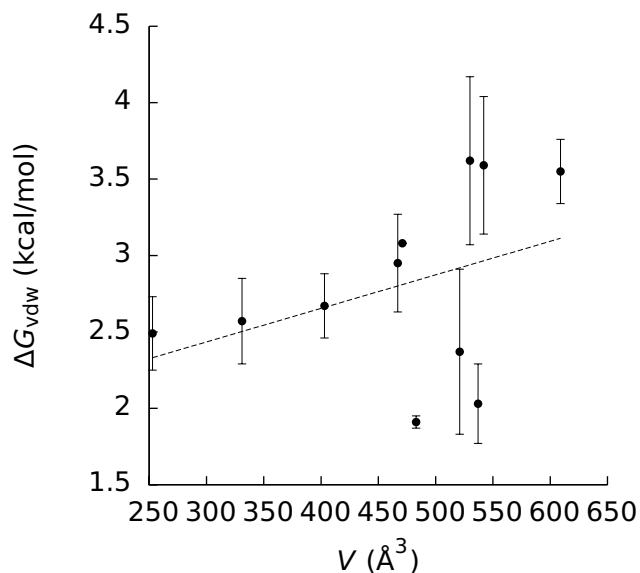


Figure 5: The energy required to form a van der Waals cavity (ΔG_{vdw}) as a function of the solvent-accessible volume (V) for the alkanes. The error bars are equal to the difference between the values obtained from forward free energy perturbation (FEP) and backward FEP.

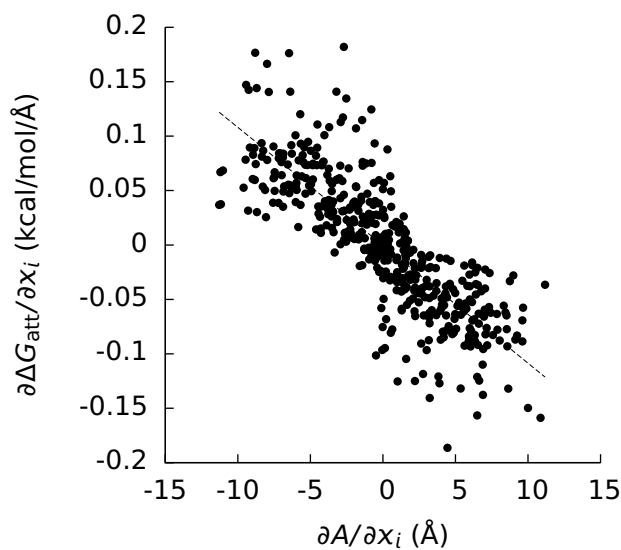


Figure 6: The derivative ($\partial\Delta G_{\text{att}}/\partial x_i$) of the attractive component (ΔG_{att}) of the energy required to form a van der Waals cavity with respect to the coordinates (x_i) of the atomic centers as a function of the derivative ($\partial A/\partial x_i$) of the solvent-accessible surface area (A) with respect to x_i for the decaalanine conformations.

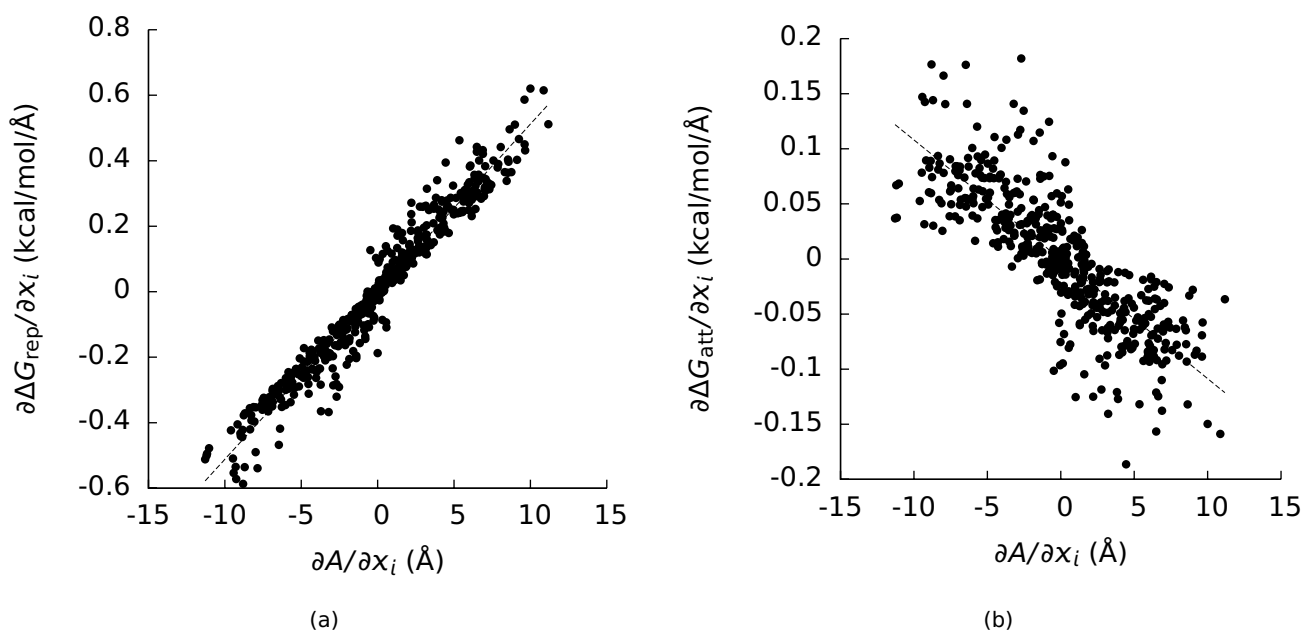


Figure 7: a) The derivative ($\partial\Delta G_{\text{rep}}/\partial x_i$) of the repulsive component (ΔG_{rep}) of the energy required to form a van der Waals cavity (ΔG_{vdw}) with respect to the coordinates (x_i) of the atomic centers as a function of the derivative ($\partial A/\partial x_i$) of the solvent-accessible area (A) with respect to x_i for the alkanes. b) The derivative ($\partial\Delta G_{\text{att}}/\partial x_i$) of the attractive component (ΔG_{att}) of ΔG_{vdw} with respect to x_i as a function of $\partial A/\partial x_i$ for the alkanes.

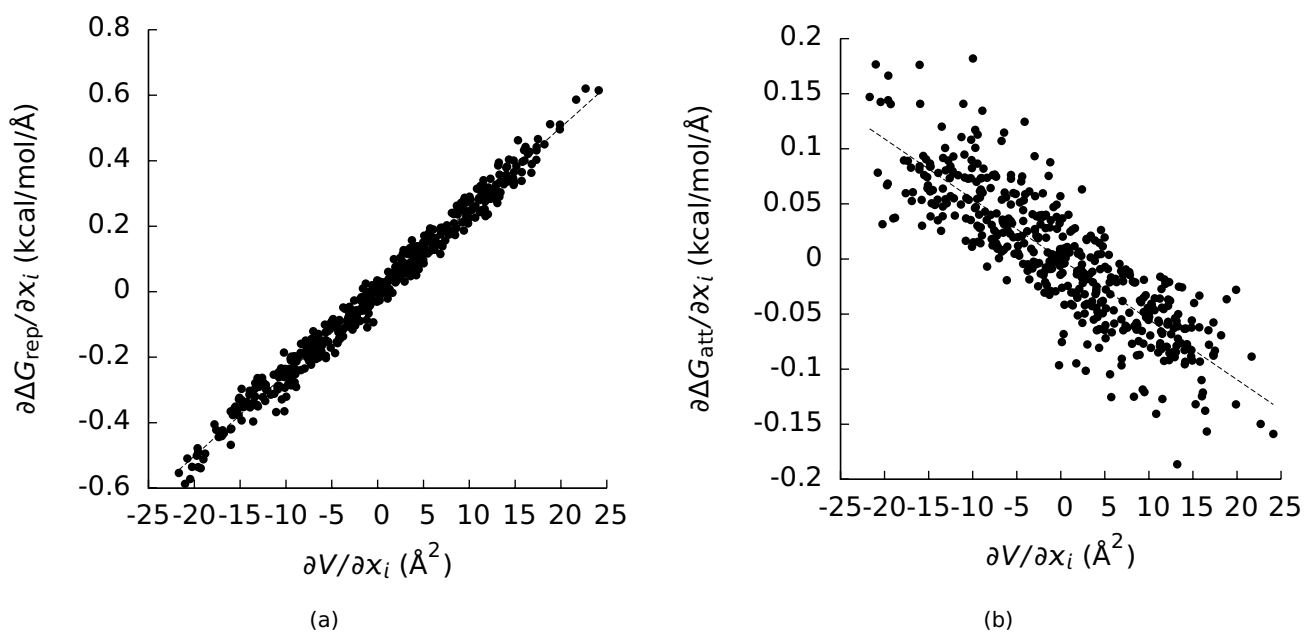


Figure 8: a) The derivative ($\partial\Delta G_{\text{rep}}/\partial x_i$) of the repulsive component (ΔG_{rep}) of the energy required to form a van der Waals cavity (ΔG_{vdw}) with respect to the coordinates (x_i) of the atomic centers as a function of the derivative ($\partial V/\partial x_i$) of the solvent-accessible volume (V) with respect to x_i for the alkanes. b) The derivative ($\partial\Delta G_{\text{att}}/\partial x_i$) of the attractive component (ΔG_{att}) of ΔG_{vdw} with respect to x_i as a function of $\partial V/\partial x_i$ for the alkanes.