

# Quantifying Solvophobic Effects in Nonpolar Cohesive Interactions

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**S** Supporting Information

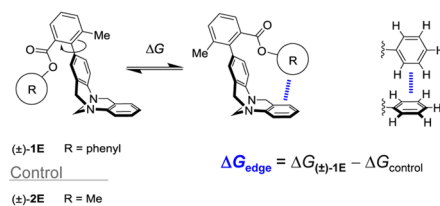
**ABSTRACT:** The hydrophobic effect plays a central role in determining the structure, activity, and properties of biomolecules and materials. In contrast, the general manifestation of this phenomenon in other solvents—the solvophobic effect—although widely invoked, is currently poorly defined because of the lack of a universally accepted descriptor. Here we have used synthetic molecular balances to measure solvent effects on aromatic, aliphatic, and fluororous nonpolar interactions. Our solvent screening data combined with independent experimental measurements of supramolecular association, single-molecule folding, and bulk phase transfer energies were all found to correlate well with the cohesive energy density (*ced*) of the solvent. Meanwhile, other measures of solvent cohesion, such as surface tension and internal pressure, gave inferior correlations. Thus, we establish *ced* as a readily accessible, quantitative descriptor of solvophobic association in a range of chemical contexts.

The hydrophobic association of nonpolar solutes in aqueous solution demonstrates the intrinsic role that a solvent can play in driving self-assembly processes.<sup>1</sup> Though the origins and defining characteristics of the hydrophobic effect are long-standing subjects of debate,<sup>1b,2</sup> the minimization of solvent-exposed nonpolar surface area can be most simply rationalized as arising from the outcompetition of solvent–solute interactions by cohesive solute–solute interactions.<sup>1,3</sup> The general manifestation of this phenomenon in other solvents can be called the solvophobic effect, with solvent cohesion having both electrostatic and van der Waals dispersion contributions.<sup>4</sup> The solvophobic effect has been invoked as governing the rate and outcome of chemical reactions<sup>5</sup> while also being exploited in supramolecular, self-assembly,<sup>6</sup> and functional materials.<sup>7</sup> Solvophobic effects are of unquestionable importance in certain fluorocarbon/aqueous/organic combinations<sup>8</sup> and in ionic liquids,<sup>9</sup> but their role is less clear away from the immiscible extremes. For example, there have been contrasting views on whether solvophobic self-assembly requires solvents that form H-bond networks.<sup>4b,9,10</sup> The role of solvophobic effects may be further obscured by other non-covalent interactions, particularly those whose magnitudes scale with molecular surface area, such as dispersion interactions.<sup>3b,6d,f,11</sup> Thus, most attributions of the solvophobic effect are qualitative, and rarely have enough solvents been examined to draw firm mechanistic conclusions.<sup>2b,3b,5d,e,6f,l,m,o,8a,10,11a,c,12h,18,20</sup> Even then, there is no agreement on the parameters that can be reliably used to identify solvophobic effects.

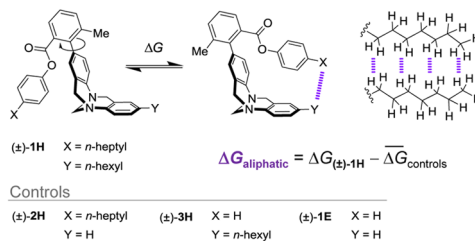
Here we examine the utility of different parameters for quantifying solvophobic effects in multiple classes of nonpolar molecular contacts. Solvophobic effects in aromatic edge-to-face, aliphatic, and fluororous interactions were measured using Wilcox torsion balances (Figures 1 to 3), and the generality of the findings was tested in a range of contexts: from the unfolding of single polymer molecules to supramolecular aromatic stacking interactions and bulk phase transfer (Figure 4).

The ambiguity surrounding the significance of solvophobic effects, particularly in organic solvents, can be largely attributed to the scarcity of solvent screening data. For example, in some solvents the interactions between nonpolar species such as those shown at the right in Figure 1 may be too weak to overcome the

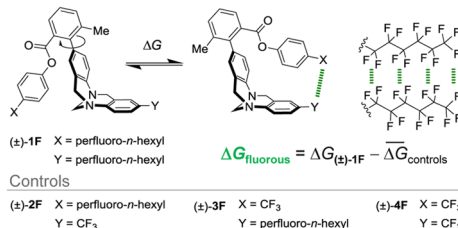
**a) Aromatic edge-to-face**



**b) Aliphatic**



**c) Fluororous**



**Figure 1.** Wilcox molecular torsion balances showing the conformational equilibria used to measure non-covalent interactions between nonpolar functional groups.  $\Delta G_{\text{controls}}$  is the mean conformational free energy of the control balances.

Received: June 3, 2015

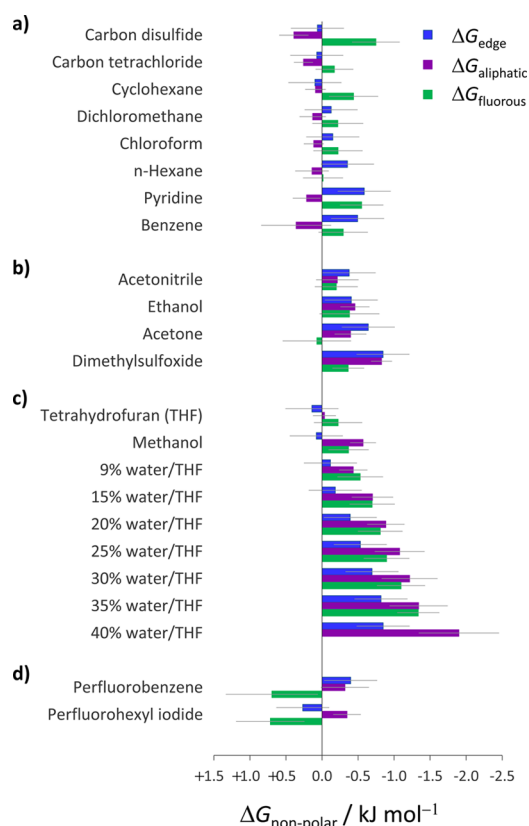
Published: July 10, 2015

entropic cost associated with bimolecular association,<sup>1c</sup> while in other cases solvophobic self-association may be so strong that the compounds of interest may not even dissolve. In addition, obtaining high-quality thermodynamic data using titration-based methods in many different solvents can be a particularly time-consuming process. Synthetic molecular torsion balances provide a means of overcoming some of the challenges associated with the measurement of non-covalent interactions.<sup>6p,q,12</sup> Most molecular torsion balances possess defined folded and unfolded conformations in which functional groups are either exposed to the solvent or brought into contact. The structures shown in Figure 1 represent archetypal molecular torsion balances of the type originally derived by Wilcox.<sup>13</sup> Since the conformational population is sensitive to the magnitude of the intramolecular interactions and the effects of the solvent, the position of a conformational equilibrium can be used as a direct measure of non-covalent interactions and solvent effects.<sup>12a,14</sup> Furthermore, rotation about the biaryl bond in the compounds shown in Figure 1 is slow on the NMR time scale (but rapid enough for equilibrium to be established in a convenient period of time). This means that the conformational free energy difference between the two conformers can be determined from a single NMR spectrum by integrating the distinct NMR peaks corresponding to each of the conformers, where  $\Delta G = -RT \ln[\text{folded}]/[\text{unfolded}]$ . Thus, molecular balances are particularly suited to examining solvent effects on weak non-covalent interactions.<sup>6l,m,12h</sup>

We set out to screen for solvophobic effects on the cohesive self-association of the nonpolar functional groups depicted in Figure 1. Although there have been numerous previous studies of aromatic edge-to-face interactions using Wilcox torsion balances, none have involved extensive solvent screens.<sup>6n,13,15</sup> To date, the general finding has been that both direct substituent–aryl and polar CH–aryl interactions make the largest contributions to the interaction energy in organic solvents.<sup>15d</sup> Thus, the unsubstituted Wilcox balance ( $\pm$ )-1E was used in the present study (Figure 1a), since any investigation of solvophobic effects on aromatic edge-to-face interactions should seek to minimize electrostatic contributions.

To account for the multiple factors contributing to the position of the conformational equilibrium in each solvent,<sup>12a,14</sup> the strength of the edge-to-face interaction,  $\Delta G_{\text{edge}}$ , was estimated by subtracting the conformational free energy of the control compound ( $\pm$ )-2E (in which the aryl ring was replaced by a methyl group) from that of ( $\pm$ )-1E.<sup>13b,16</sup> Similarly, nonpolar alkyl–alkyl ( $\Delta G_{\text{aliphatic}}$ ) and perfluoroalkyl–perfluoroalkyl interactions ( $\Delta G_{\text{fluorous}}$ ) were measured in Wilcox balances ( $\pm$ )-1H and ( $\pm$ )-1F, respectively, against the control compounds shown in Figure 1b,c.<sup>6l,m</sup>  $\Delta G_{\text{edge}}$ ,  $\Delta G_{\text{aliphatic}}$ , and  $\Delta G_{\text{fluorous}}$  were measured in 23 different solvents (Figure 2).

All three classes of nonpolar interactions examined were found to be weak, lying in the range of +1 to –2 kJ mol<sup>-1</sup>. The aromatic edge-to-face interaction measured in chloroform was similar to that previously determined in other supramolecular systems.<sup>17</sup> All three classes of nonpolar association were most favored in polar solvents (Figure 2), pointing to a role of cohesive solvent-solvent (solvophobic) effects. Thus, parameters describing cohesive solvent interactions may be useful for quantifying solvophobic association. Various parameters have been proposed to describe cohesive solvent interactions: surface tension ( $\gamma$ ),<sup>3c,6o</sup> internal pressure ( $P_i$ ),<sup>3b,4a</sup> enthalpy of vaporization ( $\Delta H_{\text{vap}}$ ), cohesive energy density ( $ced$ ),<sup>3b,20</sup> Hildebrand solubility



**Figure 2.** Bar graph showing nonpolar cohesive interactions measured in a range of solvents using the compounds and equations shown in Figure 1. Deuterated solvents were used in place of all protic solvents. Solvent mixtures are quoted in % v/v.

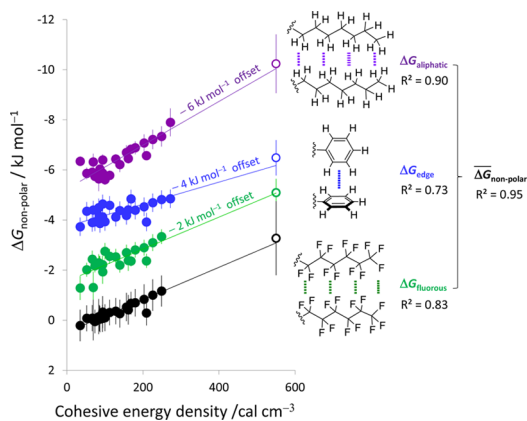
parameter ( $\delta_H$ ),<sup>18</sup> and Abraham's solvophobicity parameter ( $S_p$ ).<sup>11c</sup>  $\delta_H$ ,  $ced$ , and  $\Delta H_{\text{vap}}$  are related as follows:

$$\delta_H^2 = ced = (\Delta H_{\text{vap}} - RT)/V_m \quad (1)$$

where  $R$  is the gas constant,  $T$  is the absolute temperature, and  $V_m$  is the molar volume of the solvent.

The cohesive energy density provided the best correlations with the nonpolar interaction energies measured in the present study (Figure 3; data are offset in 2 kJ mol<sup>-1</sup> increments for clarity). This plot comprises over 200 experimental measurements of conformational free energies determined using the nine molecular balances shown in Figure 1 in 23 different solvents. However, these data correlated substantially less well with surface tension and internal pressure (Figure S6 in the Supporting Information (SI)). The former result supports earlier suggestions that surface tension may not be an ideal descriptor for hydrophobic effects.<sup>3c,19</sup> Internal pressure has been shown to be more important in the solvation of very small solutes such as gases compared with the larger interaction interfaces examined in the present study.<sup>3b</sup> Indeed, the gradients of the correlations in Figure 4a reflect a qualitative ordering of the size of the interaction interfaces.

The significant scatter associated with the correlations corresponding to individual interaction classes (colored circles in Figure 3) can be attributed to solvent-specific attenuation of dispersion and electrostatic interactions in addition to the experimental errors associated with the measurement of very weak non-covalent interactions.<sup>6l</sup> Strikingly, the mean interaction energy across all three classes of nonpolar contact reveals a

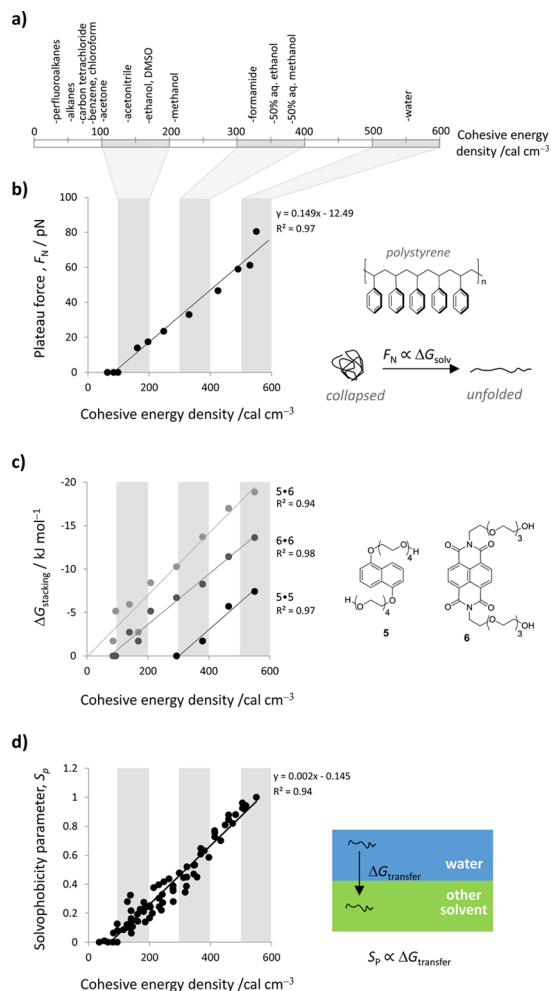


**Figure 3.** Correlations of  $\Delta G_{\text{aliphatic}}$ ,  $\Delta G_{\text{edge}}$  and  $\Delta G_{\text{fluorous}}$  (colored circles) and their average (black circles) as the cohesive energy density of the solvent is varied. For clarity, the plots of  $\Delta G_{\text{fluorous}}$ ,  $\Delta G_{\text{edge}}$  and  $\Delta G_{\text{aliphatic}}$  are offset by  $-2$ ,  $-4$ , and  $-6$   $\text{kJ mol}^{-1}$ , respectively. A version of this graph without the extrapolated water points (open circles) is shown in Figure S7a.

common solvophobic driving force for nonpolar association, providing a correlation with  $R^2 = 0.95$  (black circles in Figure 3), which arises from minimization of errors and cancellation of dispersion contributions across the interaction types. The intercepts in Figure 3 where  $\text{ced} = 0$  (i.e. no solvophobic effect) are  $\sim 0$   $\text{kJ mol}^{-1}$ . This is consistent with minimal electrostatic contributions and the generalized cancellation of dispersion interactions in solution.<sup>3b,6l,m,11a,12k</sup>

To test the generality of the cohesive energy density as a scale for describing solvophobic association (Figure 4a), we have replotted experimental data previously obtained in a range of solvents for both the collapse of single polystyrene molecules (Figure 4b)<sup>60</sup> and supramolecular aromatic stacking interactions (Figure 4c).<sup>20</sup> The data shown in Figure 4b represent the plateau force required to unfold a collapsed single polystyrene molecule in solution, which is directly proportional to the solvation free energy per monomer ( $\Delta G$ ).<sup>60</sup> These data had previously been plotted against solvent surface tension differences, giving a good but notably lower quality correlation (Figure S8) than that shown in Figure 4b. Figure 4c shows a plot of experimental aromatic stacking interaction energies plotted against the cohesive energy densities of the solvents examined. A subset of these data had previously been correlated against the  $E_T(30)$  solvent polarity scale,<sup>21</sup> yielding a correlation with  $R^2 = 0.88$  (Figure S9a). However, all three of the original data sets can now be correlated against cohesive energy density, giving  $R^2$  values ranging from 0.94 to 0.97 (Figure 4c). The offset intercepts can be attributed to differences in electrostatic/dispersion interactions as the complexes are varied. Plots of these data against Abraham's solvophobicity parameter  $S_p$ <sup>11c</sup> yielded equally pleasing correlations with  $R^2 = 0.93$ – $0.97$  (Figure S9b). As with the three nonpolar contacts measured using Wilcox balances, the aromatic stacking data did not correlate well with the solvent surface tension or internal pressure (Figure S9c,d).

The general utility of cohesive energy densities in describing solvophobic effects was further demonstrated by the strong correlations with  $S_p$  values (Figure 4d)<sup>11c</sup> and phase transfer free energies of hydrocarbons from water (Figure S10a). The quality of these relationships ( $R^2 = 0.94$ – $0.97$ ) are notable given that cohesive energy density is directly related to the *enthalpy* of vaporization (see eq 1) while the phase transfer energy (from which  $S_p$  is determined) is often dominated by *entropy*.<sup>22,23</sup> This



**Figure 4.** (a) Cohesive energy densities of common solvents. Solvent mixtures are quoted in % v/v. (b, c) Previously reported (b) plateau forces,  $F_N$ , for unfolding of single polystyrene molecules<sup>60</sup> and (c) aromatic stacking interaction energies,  $\Delta G_{\text{stacking}}$ <sup>20</sup> replotted against the cohesive energy density of the solvents in which the measurements were made. (d) Plot of Abraham's solvophobicity parameter<sup>5e,11c</sup> vs cohesive energy density.

relationship is likely to be a consequence of enthalpy–entropy compensation and the existence of a mechanistic continuum between the two thermodynamic extremes of entropically versus enthalpically dominated solvophobic effects. Indeed, the manifestation of the hydrophobic effect at both thermodynamic extremes is well-recognized.<sup>1b,4b,24</sup>

In summary, we have collated new and previously published experimental measurements of nonpolar cohesive interactions to examine the utility of several quantitative solvophobic descriptors. The collated data comprised hundreds of aromatic stacking, aromatic edge-to-face, aliphatic, and fluorinated interaction energies measured in intramolecular, intermolecular, bulk, and single-molecule contexts where solvent effects were systematically examined. All sets of solvent screening data correlated well with the cohesive energy density.<sup>25</sup> In contrast, alternative measures of solvent cohesion, such as surface tension and internal pressure, provided correlations of substantially lower quality. Thus, we propose that correlations of chemical properties with solvent cohesive energy density provide a quantitative signature for characterizing solvophobic effects.

## ■ ASSOCIATED CONTENT

## S Supporting Information

Synthetic procedures and additional data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05736.

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## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Pfizer Ltd. and MTEM Ltd. for studentships to C.A. and L.Y., respectively, and Nicholas Dominelli-Whiteley for assistance with compound characterization.

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- (16) The methyl group is not large or polar enough to form significant CH–aryl interactions in the folded conformation but is still large enough to block solvation of the aromatic face in a similar manner as the phenyl ester in the folded conformation (Figure S2).<sup>13b</sup>
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- (25) We propose that *ced* is the most useful parameter for quantifying solvophobic effects since (i) linear free energy correlations require energies (or parameters that are directly proportional to energies) to be plotted against one another [cf. the Hildebrand parameter, which has units of (energy)<sup>1/2</sup>] and (ii) Gibbs energies of phase transfer of standard solutes (from which *S<sub>p</sub>* values are derived) are not easily sourced, while enthalpies of vaporization (from which *ced* is determined) are widely reported (see SI).