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Anion-Enhanced Solvophobic Effects in Organic Solvent

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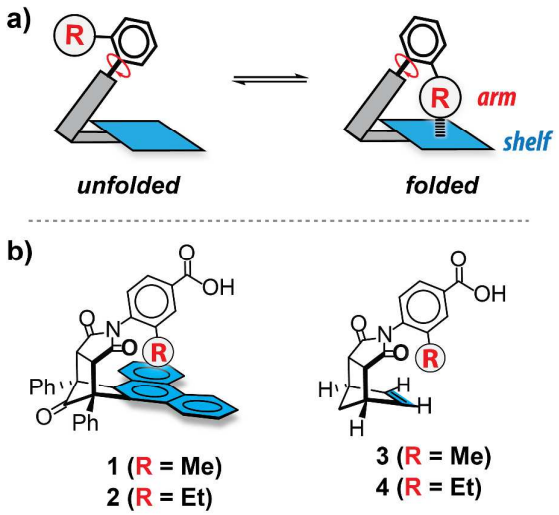
The influence of salts on the solvophobic interactions of two non-polar surfaces in organic solvent was examined using a series of molecular balances. Specific anion effects were observed that followed the Hofmeister series and enhanced the solvophobic effect up to two-fold.

Salt effects have been studied in many biological and synthetic systems including enzymes,[1,2] bacteria growth,[3] anion-receptor affinities[4–6] and protein association.[7–9] For example, the influence of salts on the solubility and stability of folded proteins was first studied by Franz Hofmeister in the late 1800's.[10–13] The influence of salts on systems that form strong anion interactions via anion binding or coordinating groups is well studied and understood.[4,5] However, salt effects in systems that lack specific anion binding groups such as the non-polar side chains of peptides is still not well understood. To study this problem in a more controlled environment, the salt effects were measured using a small-molecule model system that can form an intramolecular interaction between two non-polar surfaces: an alkyl arm and an aromatic shelf (Scheme 1). Interestingly, salts were observed to strengthen the solvophobic interactions up to two-fold in organic solvent at 1.5 M salt concentrations

The model system is a molecular torsion balance based on the *N*-arylimide framework. This versatile model system has been successfully employed to study of a wide range of weak non-covalent interactions including CH-π,[14,15] CD-π,[16] cation-π,[17] aromatic stacking,[19,18] Ag-π,[19] F-π,[20] and solvophobic interactions.[21] The *folded-unfolded* conformational equilibrium (Scheme 1a) of the balance provides a sensitive and accurate measure of the intramolecular non-covalent interactions between the molecular surfaces of the arm and shelf in the *folded* conformer. As the interaction between the arm and shelf units becomes more stabilizing, the concentration of the *folded* conformer would increase. The ratio of the *folded* and *unfolded* conformers is easily and accurately measured via integration of the ^{1}H NMR spectra. Restricted rotation of the C_{aryl}-N_{imide} single bond of the *N*-phenyl rotor leads to slow exchange and separate peaks for the *folded* and *unfolded* conformers at room temperature.

Scheme 1 (a) Representations of the *folded-unfolded* conformational equilibrium of the molecular torsional balance models used in this study. (b) Structures of molecular balances **1**-**2** and control balances **3**-**4**.



Balances **1** and **2** were designed to measure the salt effects on the solvophobic interaction between an aliphatic arm (R = Me or Et) and an aromatic phenanthrene shelf. *N*-arylimide balances with these same arm and shelf units have been shown to form stabilizing CH-π interactions in the *folded* conformer and to be sensitive probes of the solvent environments.[21–24] Control balances **3** and **4** contain the same methyl and ethyl arms as **1** and **2** but lack an aromatic phenanthrene shelf. Therefore, they form minimal intramolecular interactions in the *folded* conformer and provide a measure of the intrinsic biases of the *folded*-

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unfolded equilibrium. To improve the solubility of **1**-**4** in polar solvents, a carboxylic acid group was added to the *para*-position of the rotors.[21,24] Crystal structures of the analogs lacking the carboxylic acid solubilizing group confirmed that the alkyl arms and aromatic shelves in **1** and **2** can form intramolecular interactions in the *folded* conformers (Fig S6, ESI).[22] The crystal structures also confirmed that the alkyl arms are not able to form intramolecular interactions in the control balances **3** and **4**.

The salt effects were initially measured using acetonitrile solutions of tetrabutylammonium chloride (TBA•Cl). Significant salt effects were observed for balances **1** and **2**. For example, the folding ratio of balance **2** increased from 2.2 to 4.0 in acetonitrile solutions of 0 to 1.5 M TBA•Cl. The analogous experiment using control balances **3** and **4** saw only small changes in the folding ratios (1.2 to 1.5) on addition of TBA•Cl . The salt-induced changes in the folding ratios of **1** and **2** were surprising as these systems lack features commonly associated with salt effects.[16] Specifically, the organic solvent and the interacting surfaces of the balances (aliphatic and aromatic) do not contain anion coordinating groups such as hydrogen bond donors or positively charged surfaces. Furthermore, the salt-induced changes in ΔG_{fold} were only observed in organic solvents. The addition of even small amounts of water (3 v/v% of D_2O in acetonitrile) eliminated or greatly diminished the salt effects (*vide infra*).

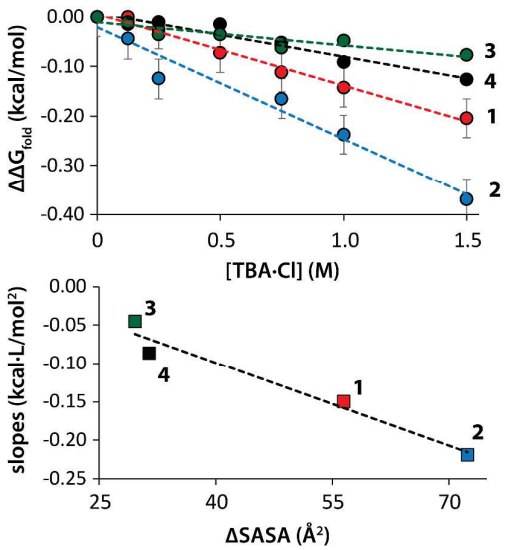

Fig 1. (a) Salt effects of balances **1**-**4** at varying TBA•Cl concentrations, as measured by the difference in folding energies ($\Delta\Delta G_{fold}$). Error bars for balances **3** and **4** are within the data markers. (b) Slopes of the salt concentration relationships for balances **1**-**4** in Fig. 1a plotted against the change in solvent accessible surface area (ΔSASA) in the *folded-unfolded* equilibria, which were calculated from X-ray structures.

The concentration dependence of the salt effects was assessed by measuring the change ($\Delta\Delta G_{fold}$) in the folding ratios for balances **1**-**4** in acetonitrile solutions containing 0 to 1.5 M TBA•Cl.[§] In each case, the solvophobic effect, as measured by the folding energies, increased linearly with increasing salt concentration (Fig 1a). Again, clear differences were observed between the balances that could (**1** and **2**) or could not (**3** and **4**) form intramolecular interactions. Balances **1** and **2** had larger salt effects than control balances **3** and **4**. Furthermore, balances with the larger ethyl arm consistently showed larger salt effects than smaller arm methyl balances (**2** > **1** and **4** > **3**).

The addition of TBC•Cl appeared to strengthen the solvophobic effect by increasing the polarity of the solvent environment. Support for this hypothesis was provided by four observations. First, the folding ratios in the *N*-arylimide balances have been shown to be excellent measures of solvent polarity and solvophobic effects.[21,23] Thus, the salt-induced changes in the folding ratios of balances **1-4** are consistent with changes in the solvent environment. Second, the salt titration plots (Fig 1a) were linear, which is indicative of a very weak or non-specific interaction such as the interaction of the salts with the solvent. In contrast, direct interactions of the salts with the folding surfaces of the balances would have yielded an asymptotic binding curve. Third, high concentrations of salts were required (> 0.5 M) to yield significant changes in the folding ratios. This is consistent with the high concentrations necessary to increase the polarity of the bulk solution.[25] Fourth, the salt effects were not dependent on the concentration of the balance. The magnitude of the salt effects was the same at lower (5 mM) or high (25 mM) concentrations. If the salts were interacting directly with the balances, then the salt effect would be dependent on the concentration of the balance.

To confirm the ability of salts to increase the solvophobic effect, the salt-induced changes in the *folded-unfolded* equilibria were correlated with the change in solvent accessible surface area (ΔSASA) for each balance.[26] Solvophobic interactions are known to scale with ΔSASA.[26,27] Thus, salt-induced increases in the solvophobic effect should also scale with ΔSASA. The ΔSASA values were calculated from the crystal structures of **1**-**4** analogs using a 1.0 Å radius solvent probe.[‡] The magnitudes of the salt effects in **1-4** were assessed from the slopes of the salt titration plots (Fig 1a), which provided a more accurate estimate than the previous single concentration measurements. A linear correlation was observed (Fig 1b) providing support that the salt-induced changes was due to a strengthening of the solvophobic effect. Again, the largest salt effects were observed for balances **1** and **2**, which form intramolecular interactions and thus had the largest ΔSASA. Similarly, the larger salt effect for the ethyl versus methyl balances (**1** > **2**) can be explained by the greater surface area contact of the ethyl group with the phenanthrene shelf in the *folded* conformer leading to a greater ΔSASA. From slope of the plot in Fig 1b, the change in the solvophobic effect in acetonitrile on addition of TBA•Cl addition to the balances was 2.9 cal/mol $Å^2$ M.

The salt-enhanced solvophobic effects in acetonitrile were calibrated against the solvophobic effects of more polar organic solvents. Balance **2** was selected for this study as it showed the largest salt and solvophobic effects. The solvophobic effects were measured for a series of organic solvents (chloroform, benzene, DCM pyridine, acetone, acetonitrile, DMF, and DMSO) by measuring the change in the folding energy in each solvent. The solvophobic interaction driving the folding of balance **2** was evident from the linearly decreasing folding energies with increasing cohesive energy density (*ced*) of the solvents (Fig. 2). Cockroft and others have shown that the *ced* solvent parameter provides an accurate estimate of the strengths of the solvophobic effects in a wide range of systems.[21,23] The solvophobic effects in balance **2** in acetonitrile are in the middle of the range of organic solvents tested. The addition of 1.5 M TBA•Cl to an acetonitrile solution of **2** increased the solvophobic effects nearly two-fold, as the folding energies decreased from -0.46 to -0.82 kcal/mol. Thus, the TBA•Cl effectively increased the *ced* of acetonitrile from 138.9 to 193.3 cal/cm^3 which is similar to the *ced* of the much more polar solvent, methanol (Fig. 2, open circle).

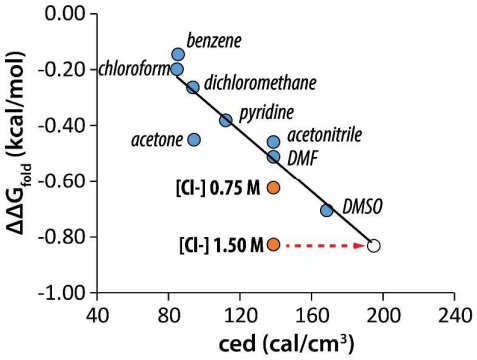

Fig 2. Measurement of the solvophobic effects on the folding energies of balance **2** in various solvents (blue circles) using the solvent cohesion parameter, *ced*. The folding energies of balance **2** in acetonitrile salt solutions in the presence of 0.75 and 1.5 M concentrations of TBA•Cl (orange circles). Estimated solvophobic effect of the 1.5 M TBA•Cl acetonitrile solution as measured by the solvent parameter *ced* (dashed red line). Estimated solvophobic effect for methanol based on the literature *ced* value of 193.3 (open circle).

Next, the anion specificity of the solvophobic enhancement was examined. The differences in the folding energy of balance **2** were measured in the presence of the TBA salts of five common anions (Cl^-, SCN^-, NO_3^-, Br^-, and ClO_4^-).[§§] Specific anion effects were observed (Fig. 3), as the anions enhanced the solvophobic effect to varying degrees that generally followed the Hofmeister anion series. The most charge-dense anion, Cl^-, showed the largest anion effects, and anions with lower charge densities showed systematically smaller anion effects. The specific anion effects were plotted against various anion parameters including hydrogen bond basicity (β), and ionic surface tension increments. An almost perfect correlation (R^2 = 0.99) (Fig 3a) was observed using the solvation energies of the anions in acetonitrile ($\Delta G_{solv.}$).[28] This provided further support for the hypothesis that the anions are enhancing the solvophobic effect by changing the bulk solvent properties.[29] If the anion-effects were simple ion-effects, then all of the anions would have had similar anion-effects as they all are mono-anions and carry the same charge. The most charge-dense Cl^- anion has the largest acetonitrile solvation energy (-64.5 kcal/mol) and accordingly displayed the anion-effect. Conversely, the least charge-dense ClO_4^- anion has the lowest acetonitrile solvation energy (-51 kcal/mol) and exhibited the smallest anion effect.

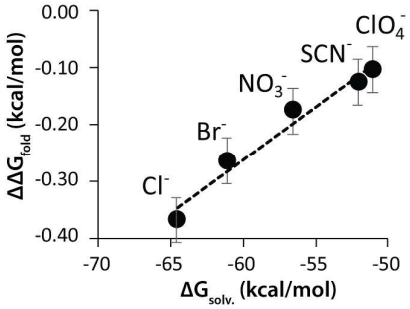

Fig 3. The measured $\Delta\Delta G_{fold}$ of balance **2** in the presence of various anions (1.5 M, acetonitrile) plotted against the acetonitrile solvation energy of the anions (ΔG_{sol}).

To confirm that the anion-effects arose from salt increasing the bulk properties of the solvent, small amounts of water were added (0 to 3% v/v) to acetonitrile solutions of balance **2** in 1.5 M TBA•Cl and 1.5 M TBA•ClO_4 (Fig. 4). The hydrogen bonding water molecules were expected to disrupt the anion effects by preferentially solvating the anions and screening their interaction with the bulk solvent. In the case of the Cl^- anion, the addition of water almost completely eliminated the anion effect. Thus, the addition of the more polar water actually reduced the solvophobic effect by 0.3 kcal/mol.[30] In contrast, the addition of water had very little effect on the anion-effects for the ClO_4^- solution. The reduction of the solvophobic effect for the Cl^- anion appeared to plateau around 3% (v/v) water addition at a similar folding energy as the ClO_4^- solution. The convergence anion effects for the charge-dense and charge-disperse anions in the presence of water suggest that the anions enhance the solvophobic effect via two mechanisms. First, the charged anions increase the solvent cohesion via increasing the ionic strength. This ionic effect is the primary mechanism for the charge-disperse anions such as ClO_4^- or the water solvated Cl^- anions and provides ~0.1 kcal/mol of additional stabilization for the *folded* conformation of balance **2**. Second, the charge-dense anions such as Cl^- can further enhance the solvophobic effect by forming interactions with adjacent acetonitrile solvent molecules. This solvent polarization appears to be increase the solvophobic effect in balance **2** by an additional 0.3 kcal/mol.

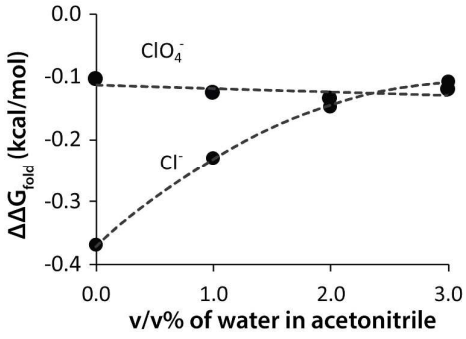

Fig 4. $\Delta\Delta G_{fold}$ of balance **2** in 1.5 M Cl^- and 1.5 M ClO_4^- acetonitrile solutions upon addition of 0-3% (v/v) water.

In conclusion, molecular balances were successfully employed as molecular probes to studysalt and anion effects in organic solvent. Anions enhanced the solvophobic effect between non-polar surfaces without direct interactions with the molecular surfaces. For example, the addition of 1.5 M TBA•Cl to acetonitrile doubled the solvophobic effect between the ethyl arm and the phenanthrene shelf. A commonly cited mechanism for similar anion effects in aqueous solutions is the interaction of the anions with water molecules, via strong charge-enhanced hydrogen bonds. Thus the observation of these anion effects in acetonitrile, which does not have any strong anion binding groups, is intriguing. Verification of the ability of anions to interact with acetonitrile and enhance the solvophobic effect was the observation of anion specific effect, which followed the Hofmeister series with higher charge density anions having a larger effect. This study demonstrates the ability of anions to tune the bulk properties of an organic solvent.

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Conflicts of interest

The authors declare no conflicts of interest.

Notes and references

§ The balance concentration for these studies was (24.5 mM). Similar anion-induced folding trends were observed at lower balance concentrations (15 mM). However, higher balance concentrations were used to provide a more accurate measure of the folding ratios via integration of the ^{1}H NMR spectra.
§§ Anions with higher charge density than Cl^- could not be assessed due to the limited solubility of their TBA salts in acetonitrile.
‡ The *folded* SASA were calculated from the arm units in contact with the shelf units in crystal structures. The *unfolded* SASA were the sum of the separately calculated SASA for arm and shelf units.

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