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How much do van der Waals dispersion forces contribute to molecular recognition in solution?**

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Author contributions:
LY and CA made equal contributions to this paper and performed all synthetic and experimental work. LY, CA and SLC analysed the data. GSN carried out X-ray crystallography. SLC conceived the experiments and wrote the paper with the input of LY, CA and GSN.

Graphical abstract:
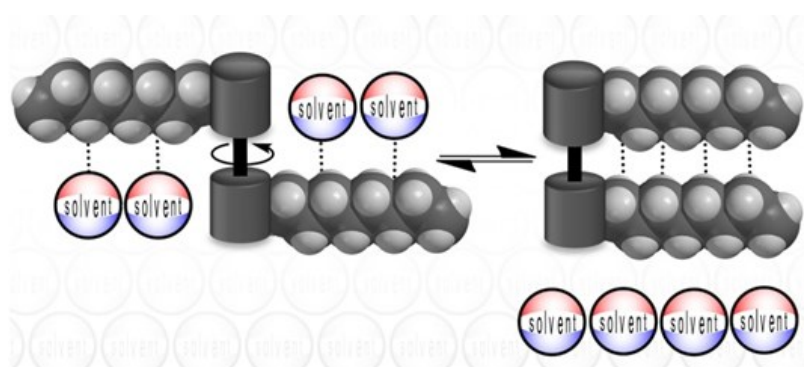
Abstract

The emergent properties that arise from self-assembly and molecular recognition phenomena are a direct consequence of non-covalent interactions. While gas-phase measurements and computational methods point to the dominance of dispersion forces in molecular association, solvent effects complicate the unambiguous quantification of these forces in solution. Here we have used synthetic molecular balances to measure interactions between apolar alkyl chains in 31 organic, fluorous and aqueous solvent environments. The experimental interaction energies are an order of magnitude smaller than estimates of dispersion forces between alkyl chains that have been derived from vaporisation enthalpies and dispersion-corrected calculations. Instead, it was found that cohesive solvent-solvent interactions are the major driving force behind apolar association in solution. The results suggest that theoretical models which implicate important roles for dispersion forces in molecular recognition events should be interpreted with caution in solvent-accessible systems.

Introduction

Dispersion forces are the attractive component of the van der Waals force that arise from correlated interactions between charge fluctuations in the electron distributions of atoms.[1] Dispersion forces have been invoked in protein folding[2] and as major factors in determining the properties of nanostructured materials;[3,4] from stabilising the longest known carbon-carbon bond[5], to governing the structure of carbon nanotubes[6] and the wetting transparency of graphene[7,8]. Beyond the molecular scale, van der Waals forces give rise to the Casimir effect[9,10], and have been implicated in the mechanisms of anaesthesia[11] and gecko adhesion[12].

Since alkanes cannot form significant cohesive polar interactions such as hydrogen bonds, the enthalpy associated with the phase transition from liquid to gas (ΔH_{vap}) can be considered as a direct measurement of the dispersion component of the van der Waals force. ΔH_{vap} changes by an average of 4 kJ mol^{-1} for each CH_2 unit added between methane and n-hexane (Supplementary Table S4). Since this energy is comparable to the strength of a hydrogen bond between two amides in chloroform[13], this conflicts with the widely held view that van der Waals interactions are weak compared to hydrogen bonds[4,14-16].

One explanation for this apparent discrepancy is that dispersion forces are difficult to measure due to complications arising from solvent effects[15,17,18]. Thus, experimental studies capable of revealing the significance of dispersion forces in solution are highly sought-after[19-23]. The unambiguous assignment of the individual factors contributing to molecular recognition requires systems that are structurally well-defined enough that the role of specific molecular contacts can be determined. Furthermore, few

supramolecular model systems are amenable to the systematic investigation of solvent effects since both solubility and association constants change dramatically as the solvent is varied. Most studies of dispersion forces have therefore been performed in the gas phase or derived from theory[16,24,25]. *Ab initio*-correlated wavefunction methods capable of modelling dispersion forces are particularly computationally demanding, and considerable research effort is being directed towards the development of DFT methods that are able to approximate dispersion forces (DFT-D)[26-28]. Moving forward, modelling dispersion forces in solution will provide an even greater computational challenge. Thus, the question remains, how much do dispersion forces contribute to molecular recognition in solution?
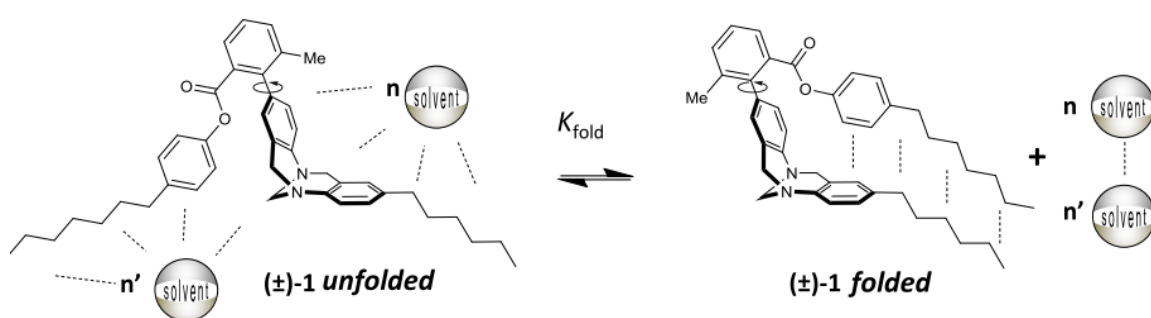

Figure 1. **Folding equilibrium for a molecular balance in solution.** The position of the folding equilibrium (K_{fold}) in molecular balance **(±)-1** is determined by the relative energies of intramolecular interactions, desolvation and solvophobic effects. If intramolecular van der Waals dispersion forces, and/or solvophobic interactions dominate then the conformer on the right-hand side of the equilibrium would be preferred. However, if solvent competition dominates then the equilibrium would lie to the left.

Molecular balances provide a useful means of measuring weak non-covalent interactions since the position of the conformational equilibrium is governed by the relative energies of intramolecular interactions and solvent interactions in the folded and unfolded conformations (Figure 1)[29,30]. In this study we have employed modified versions of Wilcox's classic molecular torsion balance, which provides a convenient framework for positioning functional groups in close proximity in the folded conformation (Figure 1)[31-34].

The key structural feature with regards to the current investigation of dispersion forces is the contact formed between the alkyl chains in the folded conformation of molecular balance **(±)-1** (Figure 1). This extended alkyl-alkyl contact is intended to maximise the contribution of dispersion forces on the position of the conformational equilibrium, while electrostatic effects are expected to be minimal due

to the apolar nature of the alkyl chains (Supplementary Fig. S11). Pleasingly, our X-ray crystal structure of compound (±)-1 confirmed that the alkyl chains are able to come into contact in the folded conformation (Figure 2a).
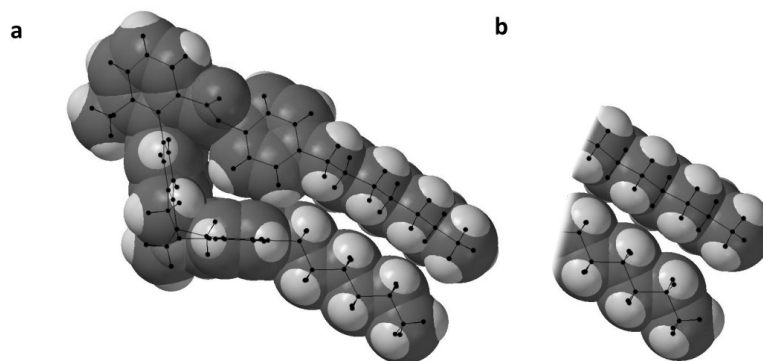
*Figure 2.* **The crystal structure of compound (±)-1 showing alkyl-alkyl contacts.** a) The structure (CCDC deposition number 898520) shows that the alkyl chains in compound (±)-1 are able to come into contact in a geometry close to a conformational energy minimum. This is evidenced by the fact that the alkyl-alkyl contact in compound (±)-1 closely resembles that found in an unrelated compound in the Cambridge Structural Database (as shown in b).[35]

Although some disorder is observed (see Supplementary Information), the similarity of this contact to others found in the Cambridge Structural Database (Figure 2b) suggests that balance (±)-1 is able to accommodate an alkyl-alkyl contact that lies close to a conformational energy minimum.[35]

In common with many other molecular balances, the Wilcox balance features a slowly rotating bond that gives rise to distinct NMR signals corresponding to the unfolded and the folded states. Each peak can be integrated to determine the free energy difference between the two conformers in a range of solvents using $\Delta G = -RT \ln K_{\text{fold}}$[29]. However, the folding free energy of compound (±)-1 alone is not sufficient to measure the free energy associated with formation of the alkyl-alkyl contact, since the position of the conformational equilibrium may also be influenced by the edge-to-face aromatic interaction in the folded conformation and other secondary interactions and solvent effects[32,34,36,37]. Thus, control compounds (±)-2 to (±)-4 were also synthesised such that the contribution of the alkyl-alkyl contact to the folding free energy could be determined as the solvent was varied.

Thermodynamic double-mutant cycles provide one possible approach for dissecting-out the magnitude of the alkyl-alkyl interaction energies as the solvent is varied (Figure 3)[32-34,38]. Application of this approach assumes that the structure of the core of the balance is unperturbed by the removal of alkyl

substituents in the control balances, and that the free energy of the alkyl-alkyl interaction and secondary effects on the position of the balance are approximately additive.[38] The validity of the structural requirement at the core of the molecular balance is supported by crystallographic data from the current study which is similar to that of other phenyl-substituted Wilcox torsion balances[32-34]. Support for the approximate additivity of the interacting components comes from previous studies that have employed double-mutant cycles in combination with Wilcox torsion balances [32-34], combined with the small differences in the experimental folding free energies of the control balances (±)-2 to (±)-4 (Figure 4). This is consistent with the very small changes in the electrostatic potentials of phenyl rings upon substitution with alkyl groups (minima change from –89 to –95 kJ mol^{-1} and maxima change from +65 to +60 kJ mol^{-1}, Supplementary Fig. S11).
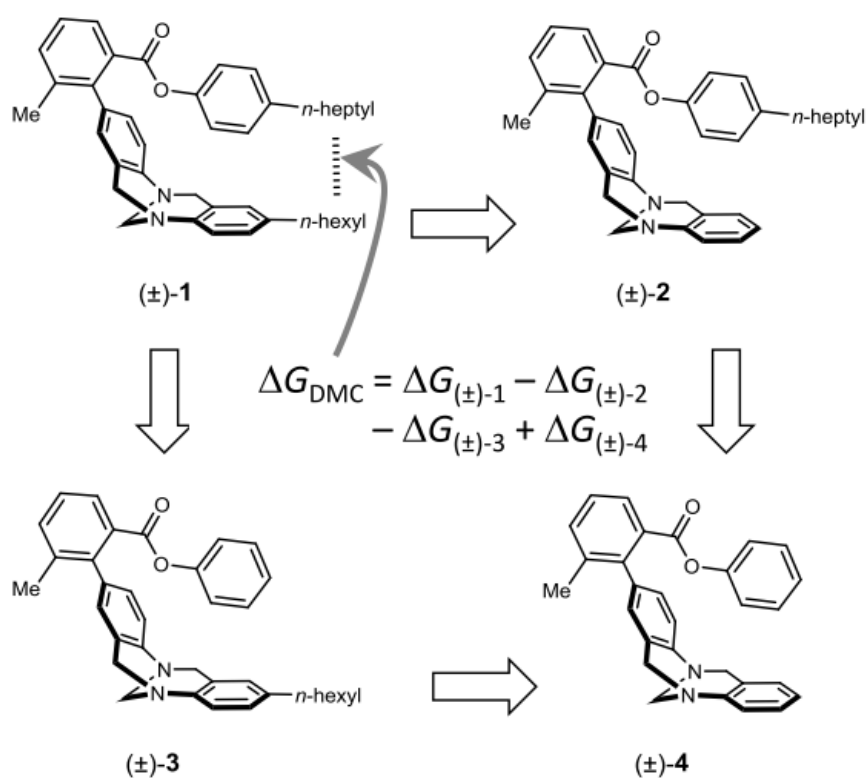
Figure 3. Thermodynamic double-mutant cycle used to isolate experimental alkyl-alkyl interaction energies (ΔG_{DMC}). An estimate of the alkyl-alkyl interaction energy of interest can be made by chemical mutations that remove it. A single mutation (e.g. comparing the folding free energy of compound (±)-1 to that of either compound (±)-2, or (±)-3) could be sufficient, but such an approach may not take into account secondary effects such as a change in the strength of the aromatic edge-to-face interaction upon removal of an alkyl chain. The folding energy of the double-mutant compound (±)-4 allows any such secondary effects to be quantified, and thus, the free energy difference of any two parallel mutations equates to the dissected alkyl-alkyl interaction energy in the presence of any associated solvent effects.
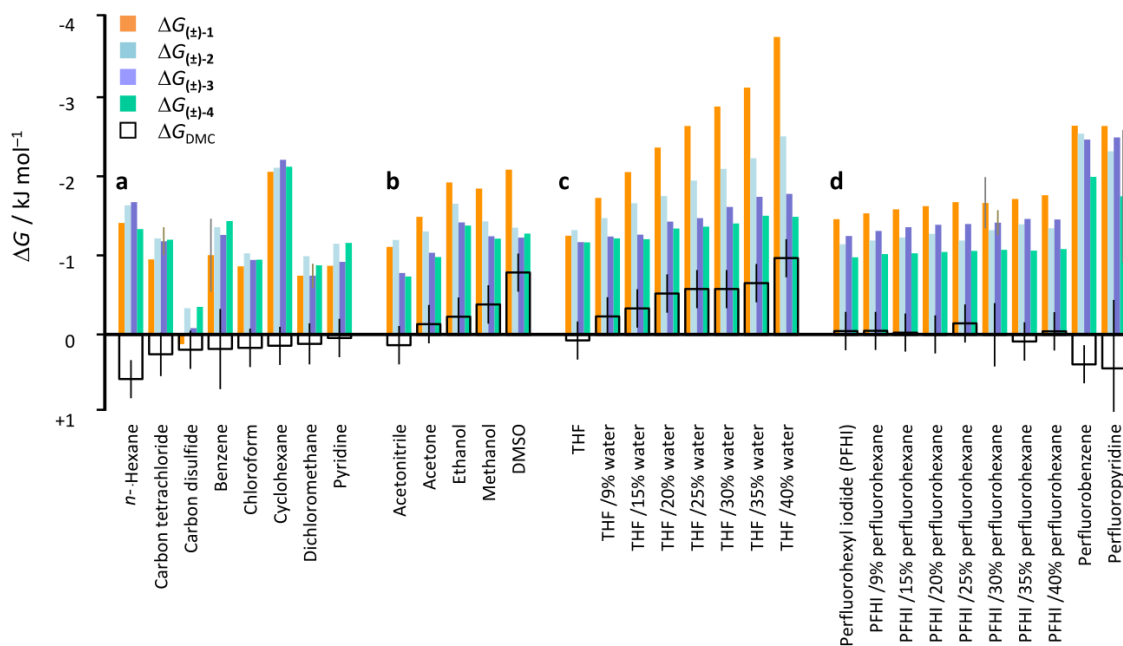
Figure 4. **Experimental folding free energies (ΔG) for compounds (±)-1 to (±)-4 (coloured bars) and alkyl-alkyl interaction energies (ΔG_DMC) dissected using the equation shown in Figure 3 (hollow black bars)**. The small magnitude of the dissected alkyl-alkyl interaction energies are particularly notable when compared to the much larger energies associated with experimental enthalpies of vaporisation for alkanes and computational estimates of alkyl-alkyl interactions in the gas-phase. Deuterated solvents were used in place of all protic solvents. Free energies have an error of $< \pm 0.12$ kJ mol^{-1} unless indicated otherwise, and relate to the error associated with integration of NMR peaks (see Supplementary Information for details). Similar magnitudes and solvent trends are seen when alkyl-alkyl interaction energies were dissected using an alternative approach (See Supplementary Information and Fig. S1, Table S1 for details). Percentages refer to (v/v) solvent mixture. DMSO corresponds to dimethylsulfoxide and THF to tetrahydrofuran.

Furthermore, an alternative method of dissecting alkyl-alkyl interaction free energies gave similar energies and trends to those obtained via the double-mutant cycle approach (see Supporting Information for details).

Results and discussion

The experimental folding energies of compounds **(±)-1** to **(±)-4** were determined in 31 different solvents and solvent mixtures. The most immediate observation arising from the analysis is that the alkyl-alkyl interaction energies dissected using the double-mutant cycle approach (ΔG_DMC) are all

small in magnitude (hollow black bars in Figure 4). Alkyl-alkyl interactions are found to be slightly disfavoured in apolar organic solvents (less than +1 kJ mol^{-1}) (Figure 4a), but slightly favoured (up to –1 kJ mol^{-1}) in the more polar organic solvents (Figures 4b). The measured alkyl-alkyl association energy was still only ~ –1 kJ mol^{-1}, in tetrahydrofuran(THF) / 40% D_2O (v/v) solution (which equates to 75 mol% of D_2O) where hydrophobic effects are likely to make a large contribution to the folding free energies (Figure 4c) [39,40,41].

The small alkyl-alkyl interaction energies measured here contrast greatly with estimates of dispersion interactions derived from enthalpies of vaporisation (ΔH_{vap} = 29 kJ mol^{-1} for n-hexane, Supplementary Table S4), and *ab initio*-correlated, and DFT-D calculations (which predict hexane dimers to have a stability of approximately –14 kJ mol^{-1} in the gas-phase)[42,43]. Similarly, calculations performed on alkanes containing enforced intramolecular alkyl-alkyl contacts (where solvent molecules cannot interpenetrate), have also shown that dispersion forces must be taken into account in the accurate prediction of bond energies[5]. In direct contrast, gas phase DFT-D methods dramatically overestimate favourable folding free energies for our solvent-exposed molecular balances by tens of kJ mol^{-1} [27,28], but the predictions of standard Hartree Fock and DFT/B3LYP methods (which do not take dispersion forces into account) are much closer to the experimentally determined folding free energies (Supplementary Table S3).

The most likely explanation for the order of magnitude difference between the very small alkyl-alkyl interaction energies measured in this study compared to the large energies derived from enthalpies of vaporisation and computational methods is that dispersion forces are effectively cancelled by competitive dispersion interactions with the solvent, although other factors that might contribute to the large energy differences should also be considered. Firstly, the enthalpy of vaporisation involves breaking dispersive contacts on all sides of a molecule on the transition from solution to the gas phase, while alkyl-alkyl contacts can only be formed on one face of each alkyl-chain in compound (±)-1. Secondly, computational alkyl-alkyl energies do not take into account entropy, while the alkane chains in compound (±)-1 have a high degree of conformational flexibility, and thus may not always be in contact in solution. An assessment of possible entropic contributions was made by measuring the folding free energies of balances (±)-1 to (±)-4 in ethanol-d_6 as the temperature was varied. The determined $-T\Delta S$ values were small and unremarkable,[34] being the same within error and only ranging between +0.3 to +0.9 kJ mol^{-1} (Supplementary Fig. S10 and Table S2).

Evidence for the role of solvent cohesion (i.e. solvophobic effects) in driving apolar association can be seen when dissected alkyl-alkyl interaction energies are plotted against the cohesive energy densities (*ced*) (Figure 5) and the Hildebrand solubility parameters (δ_H) of each solvent (Supplementary Fig. S13), which are related to each other and ΔH_{vap} as follows:

$$\delta_H = \sqrt{ced} = \sqrt{\frac{\Delta H_{vap} - RT}{V_m}}$$

where R is the gas constant and V_m is the molar volume of a particular solvent at temperature, T [44-46].
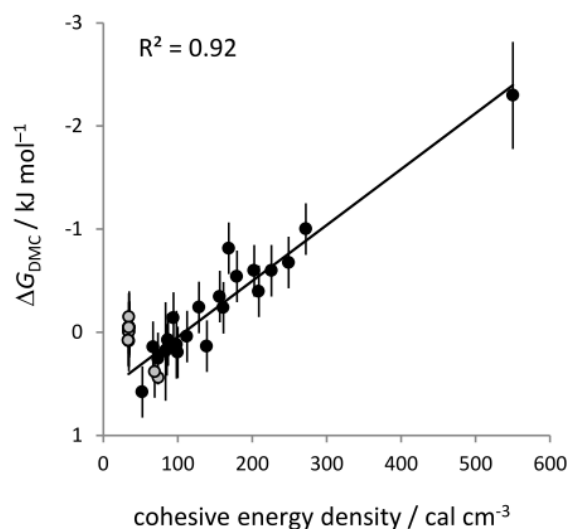
Figure 5. **Experimental alkyl-alkyl interaction free energies (ΔG_{DMC}) measured in a range of solvents with different cohesive energy densities.** Large cohesive energy densities arise due to strong cohesive interactions between solvent molecules, thus the correlation with the experimentally determined alkyl-alkyl interaction energies indicates that cohesive solvent-solvent interactions (solvophobic effects) provide a driving force for the association of apolar alkyl chains in solution. Supplementary Table S5 lists all data shown. Solid grey points correspond to perfluorinated solvents, and the R^2 value refers to all black filled points. Errors bars indicate the error associated with integration of NMR peaks (see Supporting Information for details). Due to overlapping NMR peaks, the error in ΔG_{DMC} for perfluoropyridine (ced = 74 cal cm^{-3}) is ±1.4 kJ mol^{-1} and the error bar has been omitted for clarity. The estimated ΔG_{DMC} value for D_2O (at 550 cal cm^{-3}) was extrapolated from THF/D_2O dilutions (Supplementary Figs. S2-S5).

Figure 5, shows that favourable alkyl-alkyl interactions are seen in solvents with higher cohesive energy densities (particularly in the case of dimethylsulfoxide (DMSO) and the tetrahydrofuran/water mixtures). It is interesting to note that interaction profiles derived from α_s and β_s hydrogen-bond donor and acceptor constants have previously predicted favourable alkyl-alkyl association to occur in dimethylsulfoxide as a result of solvophobic effects[13]. Indeed, the product of α_s and β_s hydrogen-bond

constants give a reasonable correlation with ΔG_{exp} for those solvents where hydrogen bond parameters are known ($R^2 = 0.80$, Supplementary Fig. S12)[13].

Perfluorinated solvents often exhibit different properties to organic solvents that are attributed to the low polarisability of fluorine atoms compared to hydrocarbons. For example, while chloroform, ethanol and acetone are immiscible with perfluorohexane, but miscible with carbon disulfide, the perfluorohexyl solvents are fully miscible with one another, but form immiscible phases with carbon disulfide (Supplementary Fig. S14). Despite these miscibility differences, the alkyl-alkyl association energies measured in the perfluorinated solvents are within error of those measured in the organic solvents (Figure 4d). Nonetheless, alkyl-alkyl association in the perfluoroalkyl solvents appear as marginal outliers on Figure 5 (*ced* ~35 cal cm^{-3}). Clearly, any influence on alkyl-alkyl association due to dispersion differences in these perfluorohexane/ perfluorohexyl iodide mixtures are small enough that they are on the limit of detection using the current approach.

In summary, we have presented experimental measurements of alkyl-alkyl interactions in solution, which appear consistent with a very large cancellation of dispersion forces due to competitive dispersion interactions with the solvent. Even though experimental enthalpies of vaporisation and high-level calculations which take dispersion forces into account show that dispersion forces are not weak in their own right, the present findings appear consistent with the view that dispersion forces are "weak" in solution, and support the hypothesis that there is little net change in dispersion forces when a molecular recognition event involves a rearrangement of the molecular surfaces in contact[13,14,18,45,47,48]. The results suggest that the degree of cancellation is only weakly dependent upon the dispersive properties of the solvent, and are in agreement with the proposal that cohesive solvent interactions (i.e. solvophobic effects) have a dominant role in driving the association of apolar groups [45]. It should be noted that the cancellation of dispersion forces is likely to be highly dependent on the solvent accessibility of the interacting molecular surfaces. As Rebek has pointed out, most organic solvents consist of approximately 45% free space[49], so a net gain in dispersion interactions may be possible when extended complementary surfaces are brought into contact[50], or when cavities within binding sites cannot be effectively solvated[4,22,23,51,52]. In addition, there is evidence to suggest that larger dispersion contributions might be seen when functional groups with higher molecular polarisabilities are brought into contact[19], particularly in solvents with lower polarisabilities. Should the conclusions derived from the present study prove to be generally applicable, then this suggests that computational models which take dispersion forces into account should be used with caution in situations where competitive dispersion interactions with the solvent can occur.

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