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Partitioning Solvophobic and Dispersion Forces in Alkyl and Perfluoroalkyl Cohesion**

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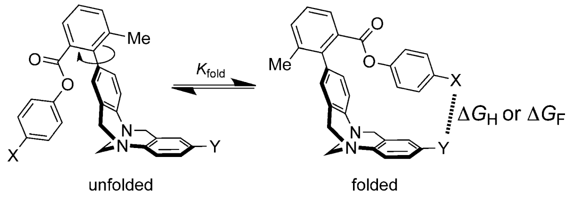
Abstract: *Fluorocarbons often have distinct miscibility properties compared to their nonfluorinated analogues. These differences may be attributed to van der Waals dispersion forces or solvophobic effects, but their contributions are notoriously difficult to separate in molecular recognition processes. Here, molecular torsion balances were used to compare cohesive alkyl and perfluoroalkyl interactions in a range of solvents. A simple linear regression enabled the energetic partitioning of solvophobic and van der Waals forces in the self-association of apolar chains. The contributions of dispersion interactions in apolar cohesion were found to be strongly attenuated in solution compared to the gas phase, but still play a major role in fluorous and organic solvents. In contrast, solvophobic effects were found to be dominant in driving the association of apolar chains in aqueous solution. The results are expected to assist the computational modelling of van der Waals forces in solution.*

The introduction of fluorine into organic compounds can have a profound influence on physiochemical properties.[1] Organofluorine chemistry plays an important role in medicinal chemistry, and is due in part to specific interactions involving fluorinated functional groups.[2] Meanwhile, fluorous synthetic strategies exploit the orthogonal miscibility of perfluorinated solvents with many organic and aqueous phases.[3] This fluorophilic/phobic effect has also been exploited in chromatographic separation,[4] proteomics,[5] carbohydrate microarrays,[6] and in the assembly of functional materials.[7] Many of the intriguing properties of organofluorine compounds can be attributed to the low polarizability of fluorine, which diminishes their ability to participate in van der Waals dispersion interactions compared to hydrocarbons.[1,2,8] However, determining the significance of dispersion forces in molecular recognition events occurring in solution is challenging because of the multiple factors contributing to noncovalent interactions.[8b,9]

Here, we seek to address this challenge in the context of alkyl–alkyl and perfluoroalkyl–perfluoroalkyl cohesion using synthetic molecular torsion balances. Molecular torsion balances have proven invaluable tools in the study of weak noncovalent interactions because of the sensitivity of conformational equilibria to solvent effects and intramolecular interactions.[2d,10] For example, derivatives of the molecular torsion balance reported by Wilcox and co-workers (Figure 1) have been used to investigate edge-to-face aromatic interactions,[11] orthogonal carbonyl interactions,[2b,c,12] the hydrophobic effect,[13] and van der Waals interactions.[10a,11b] In the Wilcox torsion balance shown in Figure 1, the hindered biaryl bond rotates slowly on the NMR timescale at room temperature, meaning that the equilibrium constant, K (and therefore the free energy difference between conformational states, ΔG), can be determined by integration of distinct peaks in ^{1}H NMR spectra corresponding to the unfolded and folded conformers.



(±)-**1H** X = *n*-heptyl
Y = *n*-hexyl

(±)-**1F** X = perfluoro-*n*-hexyl
Y = perfluoro-*n*-hexyl

(±)-**2H** X = *n*-heptyl
Y = H

(±)-**2F** X = perfluoro-*n*-hexyl
Y = CF_3

(±)-**3H** X = H
Y = *n*-hexyl

(±)-**3F** X = CF_3
Y = perfluoro-*n*-hexyl

(±)-**4H** X = H
Y = H

(±)-**4F** X = CF_3
Y = CF_3

alkyl-alkyl interaction, ΔG_{H}

$$= \Delta G_{(\pm)\text{-}\mathbf{1H}} - \left(\frac{\Delta G_{(\pm)\text{-}\mathbf{2H}} + \Delta G_{(\pm)\text{-}\mathbf{3H}} + \Delta G_{(\pm)\text{-}\mathbf{4H}}}{3}\right) \qquad (1)$$

perfluoroalkyl-perfluoroalkyl interaction, ΔG_{F}

$$= \Delta G_{(\pm)\text{-}\mathbf{1F}} - \left(\frac{\Delta G_{(\pm)\text{-}\mathbf{2F}} + \Delta G_{(\pm)\text{-}\mathbf{3F}} + \Delta G_{(\pm)\text{-}\mathbf{4F}}}{3}\right) \qquad (2)$$

Figure 1. Molecular torsion balances (±)-**1H** and (±)-**1F** form alkyl–alkyl and perfluoroalkyl–perfluoroalkyl contacts in their folded conformations respectively. Control compounds (±)-**2H**–**4H** and (±)-**2F**–**4F** in which one or both of the alkyl groups are removed allow the magnitudes of alkyl–alkyl and perfluoroalkyl–perfluoroalkyl interactions in torsion balances (±)-**1H** and (±)-**1F** to be determined using Equations (1) and (2), respectively.

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Inspired by these previous studies, we reasoned that comparing the intramolecular chain–chain interactions in (±)-**1H** and the fluorinated analogue (±)-**1F** would enable a comparative investigation of the physicochemical origins of hydrocarbon and fluorous cohesion (Figure 1). The X-ray and calculated minimized structures of the compounds (±)-**1H** and (±)-**1F** indicate that they are respectively able to accommodate extended intramolecular alkyl–alkyl or perfluoroalkyl–perfluoroalkyl contacts in the folded conformation (see Figure S2 in the Supporting Information). It follows that cohesive forces between the chains will influence the position of the conformational equilibrium, *K*, indicated in Figure 1. Since both alkyl and perfluorinated alkyl chains have particularly apolar electrostatic surface potentials (see Figure S1), interactions between the chains will be dominated by solvophobic effects and van der Waals interactions. However, perfluoroalkyl and alkyl chains should be expected to have rather different propensities to form dispersive van der Waals interactions.

The isolated folding free energies of (±)-**1H** and (±)-**1F** are not sufficient to determine the strength of cohesive interactions between the chains, since other secondary interactions and solvent effects also influence the conformational equilibrium. Nonetheless, it is possible to estimate the cohesive chain–chain interactions of interest by comparing the behavior of (±)-**1H** and (±)-**1F** to control compounds lacking one or both of the interacting chains. Previous work has shown that substituting an alkyl chain for a proton has a minimal effect on the electrostatic potential of an aromatic ring (Figure S1), thus making (±)-**2H**–**4H** appropriate controls for dissecting out the strength of alkyl–alkyl interactions in (±)-**1H** using Equation (1).[10a] Similarly, calculated electrostatic potentials show that the CF_3 group has almost identical substituent effects as a perfluorohexyl group (Figure S1). Thus, the control compounds (±)-**2F**–**4F** were synthesized as controls to measure the extended perfluoroalkyl–perfluoroalkyl interactions contained within (±)-**1F** using Equation (2).

Experimental free folding energies of (±)-**1H**–**4H** and (±)-**1F**–**4F** were obtained in 31 solvents and solvent mixtures (see Figure S4 and Tables S2 and S3). In line with previous work, the experimental energies were found to be an order of magnitude less favorable than those calculated using gas-phase methods which take dispersion forces into account (Table S1).[9e] The largest solvent-dependent folding energy variations were seen for balances (±)-**1H** and (±)-**1F**, while those of the control balances (±)-**2H/F**–**4H/F** (which lacked the ability to form intramolecular chain–chain interactions) varied to a lesser extent (Figure S4). While no method of dissecting the energetic contributions of individual functional-group interactions is ideal,[11 g 14] this observation supports the use of Equations (1) and (2) for estimating the magnitude of the alkyl–alkyl (ΔG_H) and fluoroalkyl–fluoroalkyl interactions (ΔG_F) of interest. Furthermore, errors associated with the energy dissection are fully accounted for in the error bars shown in Figure 2a since they are determined directly from the standard deviations in the energies of the control balances (see error analysis in the Supporting Information). These dissected ΔG_H and ΔG_F energies had magnitudes of $< \pm 2$ kJ mol^{-1} (Figure 2a), and are consistent with a large tempering of intramolecular dispersion forces resulting from competitive dispersion interactions with the solvent.[8b,9c,15] Thus, further analysis is required to determine whether the remaining differences in dispersion forces make any discernible contribution to the observed interaction energies.

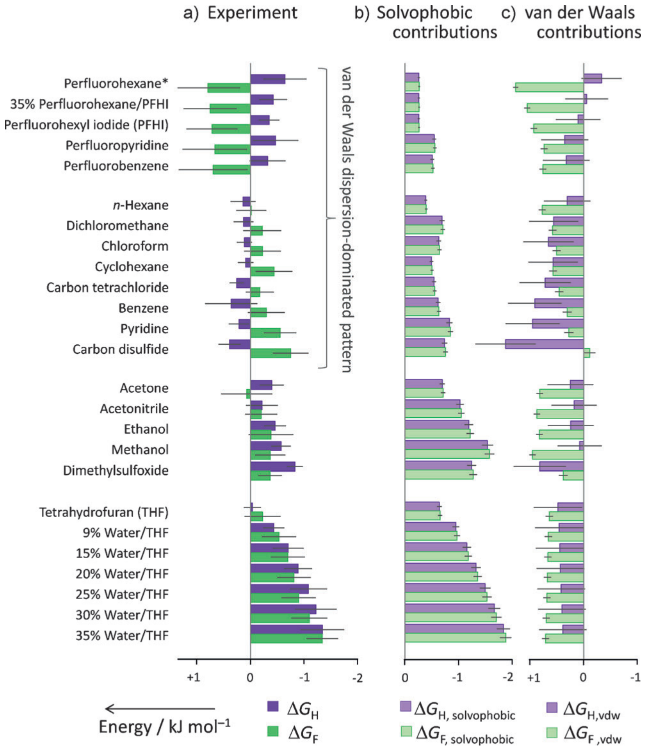

Figure 2. a) Experimental cohesive interaction energies measured between alkyl chains, ΔG_H (purple) and perfluoroalkyl chains, ΔG_F (green) using molecular balances (±)-**1H**–**4H** and (±)-**1F**–**4F** and Equations (1) and (2), respectively. All solvent mixtures are reported in vol%. b) Dissected solvophobic ($\Delta G_{solvophobic}$) and c) van der Waals (ΔG_{vdw}) free energy contributions to alkyl–alkyl (light purple) and perfluoroalkyl–perfluoroalkyl cohesion (light green), determined by fitting experimental free energies to the simple model given by Equation (3). All data, error values, and those of other solvent mixtures are presented in the Supporting Information. Deuterated solvents were used in place of all protic solvents. * The value for perfluorohexane was extrapolated from data obtained in perfluorohexyliodide/perfluorohexane mixtures (see Figures S5–S8).

Inspection of the experimental interaction energies, as the solvent is varied, provides insights into the forces driving the self-association of apolar chains. In the tetrahydrofuran/water mixtures, the alkyl–alkyl (ΔG_H) and perfluoroalkyl–perfluoroalkyl (ΔG_F) interaction energies were very similar (Figure 2a, bottom). The finding appears to be consistent with that of Whitesides et al. who found that alkyl and fluoroalkyl chains had similar hydrophobicities in carbonic anhydrase binding.[16] However, it should be noted that absolute comparison of the interaction energies is not possible in the present systems because the contact surface areas of the dissected alkyl–alkyl and perfluoroalkyl–perfluoroalkyl interactions are not necessarily the same (because of differences in the size of the F versus H atoms and differences in the lengths

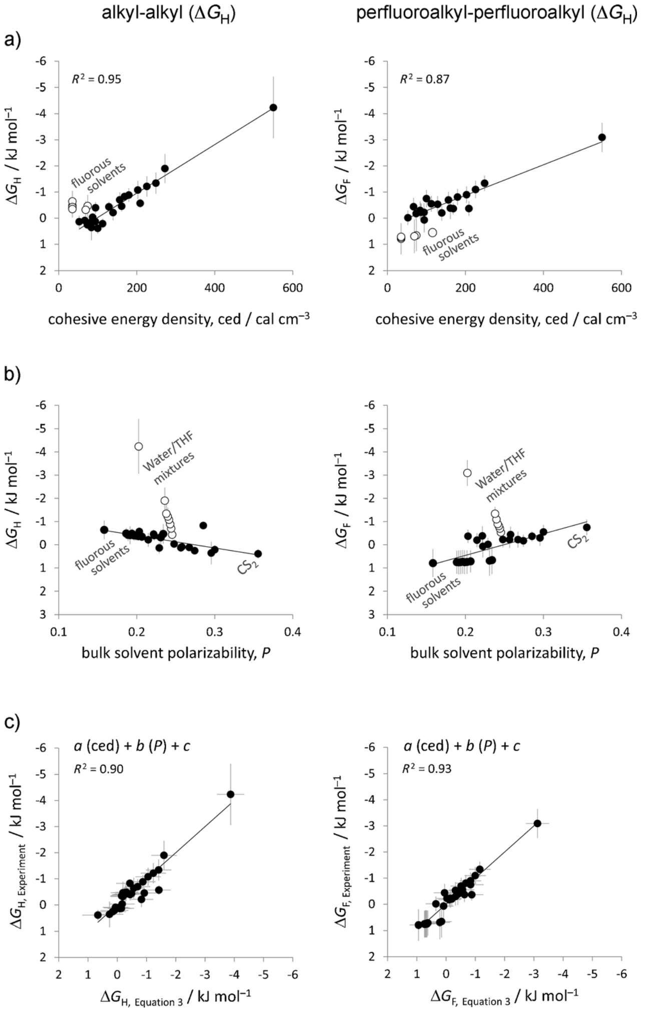

Figure 3. Correlation of experimental alkyl–alkyl (ΔG_H) and perfluoroalkyl–perfluoroalkyl (ΔG_F) interaction energies plotted against a) solvent cohesive energy density (fluorous solvent outliers indicated with hollow points), b) bulk solvent polarizability (water/THF outliers indicated with hollow points), and c) free energies predicted from linear regression analysis where both solvent cohesive energy density and bulk solvent polarizability are taken into account according to Equation (3). All plotted data and errors are provided in the Supporting Information. Bulk polarizability, P is related to molecular polarizability, α by the equation, $PV_m = 4/3\pi N\alpha$ where V_m is the molar volume and N is the number of molecules per unit volume.[19]

of the chains employed). More significant is the finding that the ΔG_H and ΔG_F values measured in the present study correlate with solvent cohesive energy density (ced) for organic and aqueous solvents (Figure 3a; see Table S4). This data is consistent with an important role for cohesive (solvophobic) solvent–solvent interactions in the self-association of alkyl and perfluoroalkyl chains.[9c,e,17]

However, solvophobic effects do not adequately explain the ΔG_H and ΔG_F values measured in fluorous solvents, which are moderate outliers (in different directions) on the cohesive energy density correlations (hollow circles, Figure 3a). Solvophobic effects are also unable to account for the symmetry inversion in the patterns of ΔG_H and ΔG_F on moving from fluorous to apolar organic solvents (Figure 2a, top left). Instead, these differences suggest an important role for van der Waals dispersion forces in governing molecular behavior, despite considerable solvent-mediated attenuation of dispersion interactions compared to the gas phase.

Molecular polarizabilities have previously been used to rationalize the role of dispersion forces in molecular interactions.[9d,18] However, the dispersive interactions of a solvent are best described by bulk polarizability, P.[19] The opposing gradients of the plots of P against ΔG_H and ΔG_F (Figure 3b, black circles) reveal the contrasting competitive influence of solute–solvent dispersion interactions on the self-association of perfluoroalkyl and alkyl chains. Meanwhile, the results obtained in water/tetrahydrofuran mixtures are outliers in Figure 3b (hollow circles) because of the large contributions from solvophobic effects.

The correlations in Figures 3a and 3b indicate that both van der Waals dispersion forces (a function of P) and solvophobic effects (a function of ced) make significant contributions to the experimental ΔG_H and ΔG_F interaction energies. Thus, a linear regression analysis of the experimental data was performed to dissect the solvophobic ($\Delta G_{\text{solvophobic}}$) and van der Waals ($\Delta G_{\text{vdw}}$) contributions to ΔG_H or ΔG_F as follows:

$$\begin{aligned}\Delta G_{H/F} &= \Delta G_{\text{solvophobic}} + \Delta G_{\text{vdw}}\\ \Delta G_{H/F} &= \Delta G_{\text{solvophobic}} + \Delta G_{\text{vdw (solv. dependent)}} + \Delta G_{\text{vdw (solv. independent)}}\\ \Delta G_{H/F} &= a\,(\text{ced}) \qquad + b\,(P) \qquad\qquad + c\end{aligned} \tag{3}$$

Each set of ΔG_H and ΔG_F values (measured in 31 different solvents and solvent mixtures; Tables S2 and S3) was independently fitted to Equation (3) to determine the corresponding a, b, and c coefficients for alkyl and perfluoroalkyl cohesion, where $a\,(\text{ced})$ encoded the $\Delta G_{\text{solvophobic}}$ term, $b\,(P)$ encoded the solvent-dependent component of ΔG_{vdw}, and c encoded the solvent-independent component of ΔG_{vdw} (i.e. direct intramolecular chain–chain interactions and sterics). Excellent agreement was seen between the experimental ΔG_H and ΔG_F values and those given by fitting to Equation (3) ($\Delta G_{\text{H/F, equation (3)}}$), thus supporting the validity of the model represented by Equation (3) ($R^2 = 0.90$ and 0.93; Figure 3c).

The dissected solvophobic [$\Delta G_{\text{solvophobic}} = a\,(\text{ced})$] and van der Waals contributions [$\Delta G_{\text{vdw}} = b\,(P) + c$] to the experimental chain–chain interaction energies are plotted graphically in Figures 2b and c as the solvent was varied. Solvophobic contributions were found to be very similar for the alkyl–alkyl and perfluoroalkyl–perfluoroalkyl contacts examined in our systems, and were dominant in polar and aqueous solvents (hence the correlations with cohesive energy density; Figure 2a). However, Figures 2b and 2c indicate that differences in dispersion interactions have a dominant influence in fluorous and apolar organic solvents (where cohesive solvent interactions are weak). This data explains the inverted symmetry of the interaction trends for perfluoroalkyl versus alkyl cohesion in fluorous and apolar solvents as the bulk polarizability of the solvent is varied (Figure 2a, top and Figure 3b).

In conclusion, we have used molecular torsion balances to measure alkyl–alkyl and perfluoroalkyl–perfluoroalkyl cohesive interactions in a wide range of solvents. A simple linear regression allowed solvophobic and van der Waals dispersion contributions to the self-association of apolar chains to be dissected. Both van der Waals interactions and solvophobic effects were found to make significant contributions to the self-association of apolar chains. As a first approximation, solvophobic effects were most important in aqueous and the highly polar organic solvents, while differences in van der Waals dispersion forces were most important in apolar organic and fluorous solvents. Comparison of the experimental data with gas-phase calculations shows that competitive solvent interactions strongly attenuate the dispersion forces between apolar chains. However, the extent of this attenuation is dependent on the bulk polarizability of the solvent, which is manifested in experimental differences in the cohesion of alkyl versus perfluoroalkyl chains as the solvent is varied. These measurements provide fundamental insights into the mechanisms of apolar self-association in solution and have implications for the fields of supramolecular chemistry, fluorous synthesis, the nanoscale assembly of materials, and the computational modelling of noncovalent interactions in solution.

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[1] D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319.

[2] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886; b) F. Hof, D. M. Scofield, W. B. Schweizer, F. Diederich, *Angew. Chem. Int. Ed.* **2004**, *43*, 5056 – 5059; *Angew. Chem.* **2004**, *116*, 5166 – 5169; c) F. R. Fischer, W. B. Schweizer, F. Diederich, *Angew. Chem. Int. Ed.* **2007**, *46*, 8270 – 8273; *Angew. Chem.* **2007**, *119*, 8418 – 8421; d) B. W. Gung, X. Xue, Y. Zou, *J. Org. Chem.* **2007**, *72*, 2469 – 2475; e) S. L. Cockroft, C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Am. Chem. Soc.* **2005**, *127*, 8594 – 8595.

[3] a) I. T. Horváth, J. Rábai, *Science* **1994**, *266*, 72 – 75; b) A. Studer, S. Hadida, R. Ferritto, S.-Y. Kim, P. Jeger, P. Wipf, D. P. Curran, *Science* **1997**, *275*, 823 – 826; c) Z. Luo, Q. Zhang, Y. Oderaotoshi, D. P. Curran, *Science* **2001**, *291*, 1766 – 1769; d) K. E. Myers, K. Kumar, *J. Am. Chem. Soc.* **2000**, *122*, 12025 – 12026.

[4] a) D. P. Curran, Z. Luo, *J. Am. Chem. Soc.* **1999**, *121*, 9069 – 9072; b) N. Marchetti, L. Caciolli, A. Laganà, F. Gasparrini, L. Pasti, F. Dondi, A. Cavazzini, *Anal. Chem.* **2012**, *84*, 7138 – 7145.

[5] S. M. Brittain, S. B. Ficarro, A. Brock, E. Peters, *Nat. Biotechnol.* **2005**, *23*, 463 – 468.

[6] K.-S. Ko, F. A. Jaipuri, N. L. Pohl, *J. Am. Chem. Soc.* **2005**, *127*, 13162 – 13163.

[7] a) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496 – 3508; b) S. Sato, J. Iida, K. Suzuki, M. Kawano, T. Ozeki, M. Fujita, *Science* **2006**, *313*, 1273 – 1276; c) S. Shimizu, T. Kiuchi, N. Pan, *Angew. Chem. Int. Ed.* **2007**, *46*, 6442 – 6445; *Angew. Chem.* **2007**, *119*, 6562 – 6565; d) V. Percec, M. Glodde, T. K. Bera, Y. Miura, I. Shiyanovskaya, K. D. Singer, V. S. K. Balagurusamy, P. A. Heiney, I. Schnell, A. Rapp, H. W. Spiess, S. D. Hudson, H. Duan, *Nature* **2002**, *417*, 384 – 387; e) J. Berná, D. A. Leigh, M. Lubomska, S. M. Mendoza, E. M. Pérez, P. Rudolf, G. Teobaldi, F. Zerbetto, *Nat. Mater.* **2005**, *4*, 704 – 710; f) E. Krieg, H. Weissman, E. Shimoni, A. Bar On, B. Rybtchinski, *J. Am. Chem. Soc.* **2014**, *136*, 9443 – 9452.

[8] a) K. J. Miller, *J. Am. Chem. Soc.* **1990**, *112*, 8533 – 8542; b) C. A. Hunter, *Chem. Sci.* **2013**, *4*, 834 – 848.

[9] a) H.-J. Schneider, *Angew. Chem. Int. Ed.* **2009**, *48*, 3924 – 3977; *Angew. Chem.* **2009**, *121*, 3982 – 4036; b) S. Granick, S. C. Bae, *Science* **2008**, *322*, 1477 – 1478; c) S. Otto, *Chem. Sci.* **2013**, *4*, 2953 – 2959; d) T. Liu, H.-J. Schneider, *Angew. Chem. Int. Ed.* **2002**, *41*, 1368 – 1370; *Angew. Chem.* **2002**, *114*, 1418 – 1420; e) L. Yang, C. Adam, G. S. Nichol, S. L. Cockroft, *Nat. Chem.* **2013**, *5*, 1006 – 1010; f) D. B. Smithrud, E. M. Sanford, I. Chao, S. B. Ferguson, D. R. Carcanague, J. D. Evanseck, K. N. Houk, F. Diederich, *Pure Appl. Chem.* **1990**, *62*, 2227 – 2236.

[10] a) I. K. Mati, S. L. Cockroft, *Chem. Soc. Rev.* **2010**, *39*, 4195 – 4205; b) M. J. Rashkin, R. M. Hughes, N. T. Calloway, M. L. Waters, *J. Am. Chem. Soc.* **2004**, *126*, 13320 – 13325; c) F. Cozzi, J. S. Siegel, *Pure Appl. Chem.* **1995**, *67*, 683 – 689; d) W. B. Motherwell, J. Moïse, A. E. Aliev, M. Nic, S. J. Coles, P. N. Horton, M. B. Hursthouse, G. Chessari, C. A. Hunter, J. G. Vinter, *Angew. Chem. Int. Ed.* **2007**, *46*, 7823 – 7826; *Angew. Chem.* **2007**, *119*, 7969 – 7972; e) S. L. McKay, B. Haptonstall, S. H. Gellman, *J. Am. Chem. Soc.* **2001**, *123*, 1244 – 1245; f) C. Zhao, R. M. Parrish, M. D. Smith, P. J. Pellechia, C. D. Sherrill, K. D. Shimizu, *J. Am. Chem. Soc.* **2012**, *134*, 14306 – 14309; g) M. Oki, *Acc. Chem. Res.* **1990**, *23*, 351 – 356; h) K. B. Muchowska, C. Adam, I. K. Mati, S. L. Cockroft, *J. Am. Chem. Soc.* **2013**, *135*, 9976 – 9979; i) I. K. Mati, C. Adam, S. L. Cockroft, *Chem. Sci.* **2013**, *4*, 3965 – 3972.

[11] a) J. C. Adrian, C. S. Wilcox, *J. Am. Chem. Soc.* **1989**, *111*, 8055 – 8057; b) E.-i. Kim, S. Paliwal, C. S. Wilcox, *J. Am. Chem. Soc.* **1998**, *120*, 11192 – 11193; c) S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497 – 4498; d) F. R. Fischer, W. B. Schweizer, F. Diederich, *Chem. Commun.* **2008**, 4031 – 4033; e) S. L. Cockroft, C. A. Hunter, *Chem. Commun.* **2006**, 3806 – 3808; f) S. L. Cockroft, C. A. Hunter, *Chem. Commun.* **2009**, 3961 – 3963; g) H. Gardarsson, W. B. Schweizer, N. Trapp, F. Diederich, *Chem. Eur. J.* **2014**, *20*, 4608 – 4616.

[12] F. R. Fischer, P. A. Wood, F. H. Allen, F. Diederich, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 17290 – 17294.

[13] B. Bhayana, C. S. Wilcox, *Angew. Chem. Int. Ed.* **2007**, *46*, 6833 – 6836; *Angew. Chem.* **2007**, *119*, 6957 – 6960.

[14] a) A. E. Mark, W. F. van Gunsteren, *J. Mol. Biol.* **1994**, *240*, 167 – 176; b) A. García Martínez, J. Osío Barcina, Á. de Fresno Cerezo, *Chem. Eur. J.* **2001**, *7*, 1171 – 1175; c) S. L. Cockroft, C. A. Hunter, *Chem. Soc. Rev.* **2007**, *36*, 172 – 188.

[15] C. A. Hunter, *Angew. Chem. Int. Ed.* **2004**, *43*, 5310 – 5324; *Angew. Chem.* **2004**, *116*, 5424 – 5439.

[16] J. Mecinović, P. W. Snyder, K. A. Mirica, S. Bai, E. T. Mack, R. L. Kwant, D. T. Moustakas, A. Héroux, G. M. Whitesides, *J. Am. Chem. Soc.* **2011**, *133*, 14017 – 14026.

[17] a) M. R. J. Dack, *Chem. Soc. Rev.* **1975**, *4*, 211 – 229; b) M. H. Abraham, P. L. Grellier, R. A. McGill, *J. Chem. Soc. Perkin Trans. 2* **1988**, 339 – 345.

[18] L. Xing, R. C. Glen, *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 796 – 805.

[19] a) C. Marquez, W. M. Nau, *Angew. Chem. Int. Ed.* **2001**, *40*, 4387 – 4390; *Angew. Chem.* **2001**, *113*, 4515 – 4518; b) R. Bosque, J. Sales, *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 1154 – 1163.