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Citation for published version:
Yang, L, Brazier, J, Hubbard, T, Rogers, D & Cockroft, S 2016, 'Can dispersion forces govern aromatic stacking in an organic solvent?', *Angewandte Chemie International Edition*, vol. 55, no. 3, pp. 912-916. https://doi.org/10.1002/anie.201508056

Digital Object Identifier (DOI):
10.1002/anie.201508056

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Angewandte Chemie International Edition

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Can dispersion forces govern aromatic stacking in an organic solvent?

Lixu Yang, John B. Brazier, Thomas A. Hubbard, David M. Rogers and Scott L. Cockroft*

Abstract: Experimental support for the dominance of van der Waals dispersion forces in aromatic stacking interactions occurring in organic solution is surprisingly limited. Here, we have examined the size-dependence of aromatic stacking in an organic solvent. The interaction energy was found to vary by ~7.5 kJ mol^{-1} on going from a phenyl-phenyl to an anthracene-pyrene stack. Strikingly, the experimental data were highly correlated with dispersion energies determined using symmetry-adapted perturbation theory (SAPT), while the induction, exchange, electrostatic and solvation energy components correlated poorly. Both the experimental data and the SAPT-dispersion energies gave high-quality correlations with the change in solvent accessible area upon complexation. Thus, the size-dependence of aromatic stacking interactions is consistent with the dominance of van der Waals dispersion forces even in the presence of a competing polarizable solvent.

Non-covalent interactions involving aromatic rings pervade chemistry and biology.[1] Aromatic stacking interactions have attracted particular interest due to their roles in nucleic acid and protein chemistry.[2] Stacking has also been widely exploited in supramolecular chemistry[3] and in the rational design of synthetic and re-engineered biological catalysts.[4] Accordingly, numerous experimental and theoretical investigations have sought to unravel the underlying physicochemical principles governing stacking interactions.[1, 5] Although different theoretical approaches give differing estimates of the precise contributions of different interaction sub-components to aromatic stacking, there is general agreement on the importance of dispersion,[5f, 6] a finding that is corroborated by gas-phase experimental data.[7] The importance of the dispersion component of van der Waals interactions is also apparent in the solid-state where polycyclic aromatic compounds display stacked herringbone crystal structures, while smaller aromatics such as benzene and naphthalene adopt edge-to-face geometries.[8] Similarly, the solubilities of polycyclic aromatic hydrocarbons decrease with size.[9] These trends can be rationalized as arising from an increase in the relative importance of attractive van der Waals dispersion forces between the aromatic faces over polar edge-to-face interactions as the size of the aromatic groups increase.[10]

While the significance of dispersion forces in the solid-state and gas-phase is undoubted, the role of dispersion forces in molecular recognition processes is complicated by solvent effects.[11] Aromatic stacking interactions present an interesting case in this regard since large van der Waals contacts can be made between the highly complementary planar surfaces, while organic solvents contain large volumes of free space. For example, chloroform consists of 47% free space.[12] Additionally, solvent structure may be locally perturbed at extended apolar surfaces.[13] Thus, aromatic stacking interactions present a case where significant net gains in dispersion interactions might prevail, even in the presence of a competing solvent.

Experimental investigations of aromatic stacking in solution have mostly examined relatively small aromatic contacts in systems where contributions from van der Waals dispersion forces might be masked by electrostatic, solvophobic, or competitive dispersion interactions with the solvent.[5i, 14] Kool has measured natural and unnatural base stacking in the context of DNA and found hydrophobic effects to be generally dominant.[14f, 15] In contrast, Schneider identified additive energy increments in charged synthetic complexes that were attributed to net gains in dispersion interactions involving aromatic contacts due to the low polarizability of the aqueous solvent.[11b, 11f, 16] Grimme has suggested that the inclusion of dispersion forces is necessary to account for stacking energies measured using molecular balances developed by Gung, even in organic solvents.[5f, 17] Meanwhile, Shimizu recently found that varying the size and polarizability of one of the aromatic rings involved in a stacking interaction had little effect on the strength of the interaction in chloroform, suggesting that the dispersion term is largely cancelled by competitive dispersive interactions with the organic solvent.[5a] Similarly, recent research from our own group has shown that dispersion forces between hydrocarbons are measurable, but very strongly attenuated in solution.[11d, 11e, 14d] Thus, the question remains whether the dispersion component of van der Waals forces make a substantial contribution to aromatic stacking in polarizable organic solvents.

Here, we have employed supramolecular complexes to examine whether dispersion forces contribute to the size dependence of aromatic stacking interactions in an organic solvent (Figures 1 and 2). We have compared our data with SAPT computations and previous measurements of aromatic stacking interactions to determine whether electrostatic, exchange, induction, dispersion, or solvent effects dominate the interaction trends as the sizes of both halves of the stacked interface are varied (Figure 2).

We set out to design a series of structurally well-defined

[*] Dr L. Yang, Dr J. Brazier, Mr. T. A. Hubbard, Dr D. M. Rogers, Dr S. L. Cockroft
EaStCHEM School of Chemistry
University of Edinburgh
Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ (UK)
E-mail: scott.cockroft@ed.ac.uk

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[**] We thank Nicholas Dominelli-Whiteley for assisting with characterization, the EPSRC (EP/H02056X/1) for financial support, and MTEM Ltd and Afton Chemical for PhD studentships L. Y. and T. A. H., respectively. This work was supported by the EaStCHEM Research Computing Facility and the Edinburgh Compute and Data Facility (ECDF) (http://www.ecdf.ed.ac.uk/).

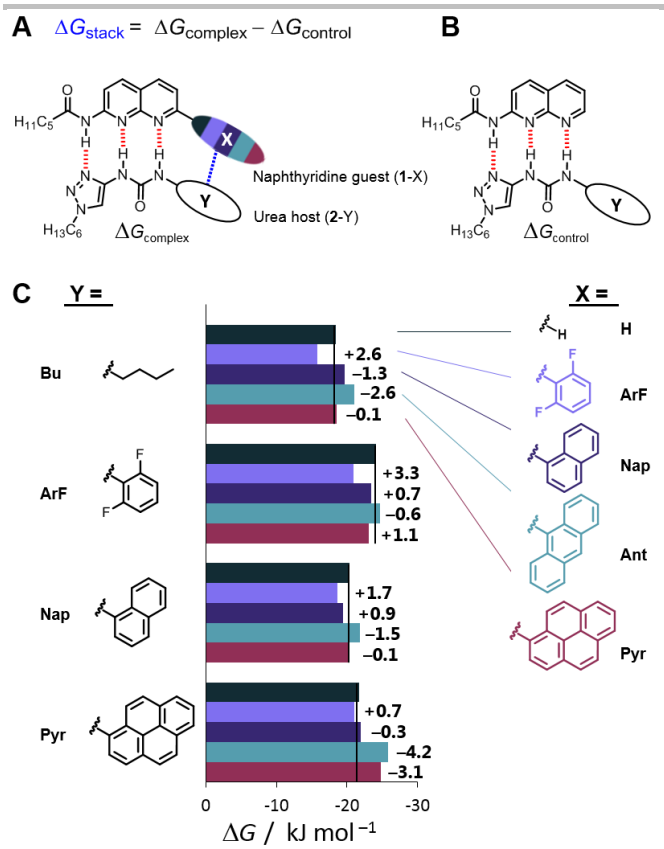

Figure 1. A) and B) Supramolecular complexes used to measure aromatic stacking interactions in solution. C) Experimental complexation free energies determined in 5% (v/v) CD_3CN in $CDCl_3$ at 298 K. Dissected experimental stacking free energies ΔG_{stack} are displayed in kJ mol^{-1} to the right of the bar for each X-Y contact (as determined using the equation shown in A). Errors in ΔG are < 1.1 kJ mol^{-1} in all cases (twice the standard error). All data and errors are provided in the SI.

supramolecular complexes that would enable systematic variation of the hydrocarbon groups brought into contact upon complexation (Figure 1A). The structures of the naphthyridine and urea partners were inspired by complexes previously developed by Zimmerman,[18] Fuentes,[19] and Wilson.[20] A series of geometry minimizations performed at various levels of theory revealed that these complex designs accommodated stacked X-Y contacts (Figures S3 to S7). Thus, five different naphthyridine guests (**1**-X) and four different urea hosts (**2**-Y) were synthesized in which functional groups X and Y were varied (Figure 1). Apolar X and Y groups were selected to minimize the contribution of electrostatic interactions to the binding free energies (Figure S1). The complexes were found to have suitable solubilities and binding constants in 5% (v/v) $CDCN_3$ in $CDCl_3$ to allow determination of thermodynamic data at room temperature using NMR titrations (see SI for experimental details).[21] Titration data for all combinations of **1**-X and **2**-Y gave high-quality fits to a 1:1 binding model (<2% error in $\Delta\delta$, Figures S10-S29), with Job plots also indicating 1:1 complexation (Figure S30). Association free energies, $\Delta G_{complex}$ for all combinations of X and Y were calculated from the fitted association constants using $\Delta G_{complex} = -RT \ln K_a$, where R is the gas constant and T is the absolute temperature. The experimental association free energies of the complexes ranged from –16 kJ mol^{-1} to –26 kJ mol^{-1} falling in the energy range of other triple H-bond complexes (Figure 1C).[22]

While no method of dissecting individual functional group interactions is ideal,[23] an estimate of the contribution of the X-Y stacking interactions to $\Delta G_{complex}$ can be obtained by subtracting the complexation free energy of the control complex where X = H for each set of complexes where Y is kept constant. These dissected ΔG_{stack} values spanned a range of 7.5 kJ mol^{-1} (labelled to the right of the bars in Figure 1C). The X = Y = difluorophenyl (ArF) complex gave the least favorable stacking interaction energy of +3.3 kJ mol^{-1}, while the most favorable energy of –4.2 kJ mol^{-1} was found in the X = anthracenyl (Ant), Y = pyrenyl (Pyr) complex. The 7.5 kJ mol^{-1} energy difference is notable given that it is equal to the strength of three OH···OH hydrogen bonds in chloroform solution[24] The data shown in Figure 1 give a qualitative indication that the X-Y interactions become more favorable as the sizes of the interacting groups increase.

To investigate the physicochemical origins of the size-related trend, symmetry-adapted perturbation theory (SAPT)[25] was used to analyze the X-Y interactions in the geometry-minimized H-bonded complexes determined at both the B3LYP/6-31G* and M06-2X/6-31G* levels (see SI for details). SAPT allows the factors contributing to intermolecular interactions to be separated into dispersion, induction, electrostatic and exchange components. More specifically, density-fitted SAPT calculations were performed at the SAPT0 level[26] using the PSI4 electronic structure program[27] with the aug-cc-pVDZ' truncated basis set[28] and frozen carbon and fluorine 1s core orbitals. Strikingly, the experimental aromatic stacking free energies ΔG_{stack} correlated most strongly with the calculated SAPT dispersion energy component for both sets of interaction geometries (R^2 = 0.95 and R^2 = 0.82) $\Delta E_{dispersion}$, blue circles in Figures 2A-B). Highly scattered or weak correlations were seen against the exchange, electrostatic and induction components, (R^2 < 0.76 in all cases). Solvation energy changes calculated using the SM8 model[29] (see SI for details) were also highly scattered when plotted against the experimental data (gray points in Figures 2A-B). The finding that only $\Delta E_{dispersion,SAPT}$ correlated well with the experimental stacking data is a strong indication that the observed interaction trend as the sizes of the aromatic X and Y groups were varied is dominated by dispersion forces, even in the presence of a polarizable organic solvent.

The change in solvent accessible area upon bringing the aromatic X and Y groups into contact was also found to be highly correlated with both the calculated $\Delta E_{dispersion}$ (R^2 = 0.98) and the experimental stacking energies ΔG_{stack} (R^2 = 0.85-0.91) (Figures 2C-D). However, such correlations might have contributions from both dispersion and the solvophobic effect.[14d] Solvent screening data for aromatic stacking previously reported by Cubberley and Iverson[14a] correlates strongly with the cohesive energy density of the solvent (*ced*), which encodes solvophobic effects arising from cohesive solvent-solvent interactions (Figure S9).[14d] The gradients of the correlations shown in Figure S9 can be normalized by the calculated change in solvent accessible area in each complex (Tables S4-S5) to estimate the solvophobic effect with the change in solvent accessible area in the solvent used in the present study. The gray wedges at the bottom of Figures 2C-D indicate the ranges of these potential solvophobic contributions (using a conservative error estimate of two standard deviations). The solvent used in the present investigation was 5% (v/v) CD_3CN in $CDCl_3$, which has a very low *ced* of 88 cal cm^{-3} (*cf.* pure chloroform = 85 cal cm^{-3}).[30] Accordingly, the gray-colored wedges in Figures 2C-D that represent the solvophobic

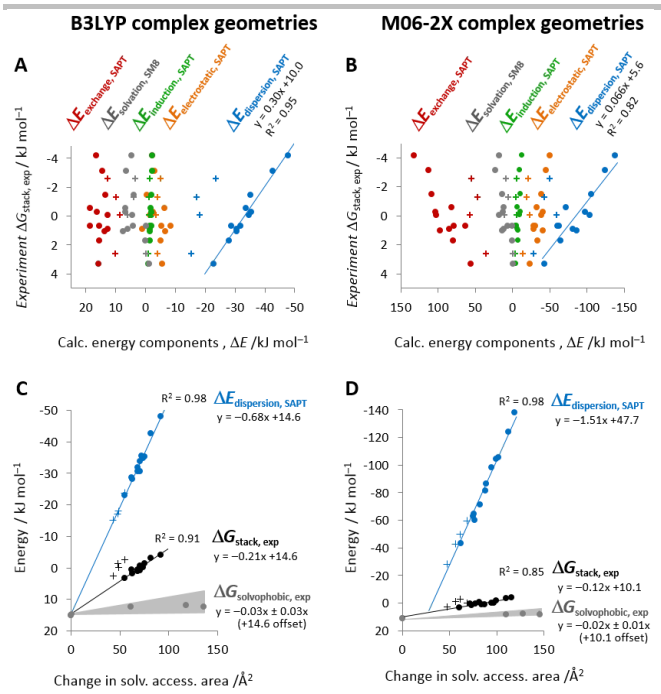

Figure 2. A) and B) Experimental stacking free energies vs. partitioned energy components for stacked X-Y geometries calculated using DF-SAPT0 with the aug-cc-pVDZ' basis set. Solvation energy changes in chloroform calculated using SM8 are also shown. The dispersion energy component correlated most strongly with the experimental data. Circles correspond to Y = aryl group while crosses are Y = *n*-butyl. C) and D) Correlation of experimental stacking free energies (black) and calculated SAPT0 dispersion energies (blue) against the change in solvent accessible area on association of X and Y in the model complexes. Solvophobic contributions were estimated from independent measurements of solvent effects on aromatic stacking interactions previously reported by Cubberley and Iverson (gray) (see Figure S9).[14a, 14d] The geometries of each X-Y interaction used in the SAPT0, SM8 and solvent accessible area calculations were determined from minimized structures of the H-bonded complexes using either the B3LYP or M06-2X level of theory and the 6-31G* basis set as indicated. The intercepts of solvophobic contributions are offset to match those of the experimental data to ease comparison of the gradients. Error bars in the experimental energies are <1.1 kJ mol^{-1} in all cases. Correlation coefficients are only shown where $R^2 > 0.76$.

estimates (offset to facilitate gradient comparison) are markedly shallow compared with our experimental stacking data (black points). The finding is consistent with data obtained for the association of similarly sized hydrocarbons, which also gave very small solvophobic contributions of <1 kJ mol^{-1} in organic solvents with *ced* values of <100 cal cm^{-3}.[11e] However, it should be noted that solvophobic effects would still be expected dominate the association of apolar aromatic groups in more cohesive solvents such as methanol/water solutions (*ced* = 209 - 550 cal cm^{-3}).[14a]

Given the small contribution from solvophobic effects in the weakly cohesive solvent used in the present investigation, the difference in the gradients of the calculated SAPT dispersion energies and the experimental data shown in Figures 2C-D indicate the degree to which dispersion forces are attenuated by the organic solvent. Since dispersion is neglected by B3LYP, but taken into account during the M06-2X geometry minimization, the data plotted in Figure 2D should provide the most representative indication of the difference between dispersion forces in the gas-phase vs. solution. The very large difference between the experimental and calculated SAPT gradients is consistent with very strong, but incomplete attenuation of dispersion forces due to solvent competition such that the size-dependence of stacking interactions is still governed by dispersion. However, it is notable that the experimental data correlates better with both the SAPT dispersion energies and the changes in solvent accessible area determined using the B3LYP complex geometries (Figures 2A and 2C) rather than the M06-2X geometries (Figures 2B and D). The implication (although this cannot be proven without a means of determining high-resolution structures in solution) is that the B3LYP-structures may more closely resemble the experimental condition in which dispersion forces are very strongly attenuated by competitive dispersion interactions with the solvent. Furthermore, the differences in the magnitudes of the calculated SAPT dispersion energies in the B3LYP (up to 50 kJ mol^{-1}) and M06-2X minimized structures (up to 140 kJ mol^{-1}) serve to underline the challenge facing the computational modelling of dispersion forces in dynamic complexes in solution where small differences in geometry can have a very large effects on the magnitude of the interaction.

Several investigators have recently questioned whether aromatic and non-aromatic hydrocarbons have distinct interaction characteristics.[5h, 6c, 31] The present study facilitates a comparison of alkyl···aryl (Y = *n*-butyl) and aryl···aryl interactions (Y = aryl group). Interestingly, the SAPT-calculated dispersion components for both *n*-butyl···aryl (blue crosses) and aryl···aryl interactions (blue circles) form single, high-quality correlations with the calculated changes in solvent accessible area (Figures 2C-D). This suggests that a difference in the dispersive properties of alkyl and aryl groups is not responsible for the experimental alkyl···aryl interaction energies being a few kJ mol^{-1} more favorable than aryl···aryl interactions involving similar changes in solvent accessible area (black crosses and circles, respectively in Figures 2C-D). Further insight can be gained from the SAPT energy decomposition data plotted in Figures 2A-B, which reveal that the minimized alkyl···aryl interactions are consistently less repulsive than the aryl···aryl contacts examined in the present study ($\Delta E_{exchange}$, red crosses and circles respectively). Indeed, an *n*-butyl chain has sufficient flexibility that the repulsive (steric) exchange interactions imposed by the H-bonded part of the complex can be minimized, while the aromatic groups are substantially more rigid. Furthermore, such flexibility differences between alkyl-aryl and aryl-aryl stacking might be manifested entropically. The result is commensurate with previous experimental[10b, 11e, 32] and theoretical studies[6c, 31, 33] that have also found similarly sized alkyl···aryl and aryl···aryl interactions to have similar stabilities.

In summary, a new class of supramolecular complex has been developed for measuring the size-dependency of aromatic stacking in organic solution. The interaction energies were found to span a range of 7.5 kJ mol^{-1} from a phenyl-phenyl to an anthracene-pyrene stack. A theoretical energy decomposition analysis was performed using symmetry-adapted perturbation theory (SAPT), and the experimental data were found to be highly correlated with only the dispersion component of the interaction. Both the SAPT-calculated dispersion energies and the experimental data correlated strongly with the change in solvent accessible area determined from calculated structures of the stacked complexes. Despite the strong attenuation of dispersion forces by competition with a polarizable organic solvent, the results suggest that dispersion forces can govern aromatic stacking in an organic solvent. We hope that these measurements will assist the development of theoretical approaches for modelling non-covalent interactions in solution.

Keywords

●molecular recognition ● aromatic interactions ● supramolecular chemistry

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Layout 2:

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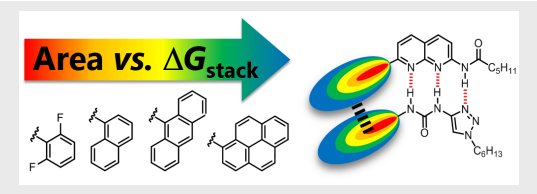

Size Matters: Dispersion forces govern the stacking interactions even in the presence of a competitive polarizable organic solvent.

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Can dispersion forces govern aromatic stacking in an organic solvent?

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