Hydrogen bonding properties of non-polar solvents†

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Received 7th October 2009, Accepted 25th November 2009
First published as an Advance Article on the web 27th January 2010
DOI: 10.1039/b921003b

A combination of high-throughput NMR titration experiments, UV-Vis absorption titrations and data collected from the literature on 1 : 1 H-bonded complexes has been used to characterise the H-bond properties of non-polar organic solvents: alkanes, perfluorocarbons, aromatic and halogenated organic solvents. The results are analysed in the context of the electrostatic solvent competition model, which assumes that solvent effects on intermolecular interactions can be interpreted based on the exchange of specific functional group contacts, with minimal involvement of the bulk solvent. For solvents where the H-bond parameters have been measured as solutes in carbon tetrachloride solution, the H-bond parameters measured here for the same compounds as solvents are practically identical, *i.e.* solute and solvent H-bond parameters are directly interchangable. For the very non-polar solvents, alkanes and perfluorocarbons, the experimental H-bond parameters are significantly larger than expected based on calculated molecular electrostatic potential surfaces. This suggests an increase in the relative importance of van der Waals interactions when electrostatic effects are weak, but there is no detectable difference between the solvation properties of cyclic and linear alkanes, which have different van der Waals interaction properties.

Introduction

Solution chemistry is highly dependent on the solvent, and a range of different solvent parameters have been developed in order to estimate solvent effects on a variety of different types of process.[1–3] These parameters are based on the effect of bulk solvent on the properties of a specific spectroscopic or reactivity probe and have been widely used to construct quantitative structure–activity relationships to describe solvation.[4–6] The properties of a system of interest can be related to a linear combination of solvent parameters, which represent H-bond donor/acceptor properties, polarisability, cohesive energy density *etc*.[7] We recently proposed an alternative approach based on individual binding site interactions at specific points on the surfaces of the solvent and solute.[8] This electrostatic solvent competition model is embodied in eqn (1).

$$\Delta G = -(\alpha - \alpha_s)(\beta - \beta_s) + c \quad (1)$$

where α and β are the H-bond donor and acceptor parameters of the solutes, α_S and β_S are the H-bond donor and acceptor parameters of the solvent and c is a constant, which was experimentally determined to be 6 kJ mol^{-1} in carbon tetrachloride solution.

The idea is that the influence of solvent on solution phase equilbria can be understood as a simple competition between four surface site contacts: one solute–solute, two solute–solvent and one solvent–solvent interaction. The values of α, β, α_S and β_S are based on Abraham's α_2^H and β_2^H scales, which were derived from experimental measurements on H-bonded complexes involving a wide range of functional groups in carbon tetrachloride and 1,1,1-trichloroethane.[9–12] Thus the H-bond parameters that describe the surface contact sites of both the solute and solvent are based on the properties of the individual isolated molecules. We assume that the intermolecular interaction properties of solvent molecules that constitute a bulk liquid are the same as the properties of the individual molecules in a dilute solution or the gas phase. Taft developed a set of empirical solvent H-bond parameters to quantify the H-bond properties of the bulk liquid, and Abraham has shown that the Taft solvent β scale correlates well with the solute β_2^H scale, which provides some experimental support for this assumption.[13] We have used eqn (1) to estimate the stability of H-bonded complexes in a variety of different solvents, and with exception of alcohols, the predictions agree extremely well with experiment.[14]

One class of functional groups for which no experimental data are available are the very non-polar groups that can not compete with carbon tetrachloride or 1,1,1-trichloroethane for the formation of H-bonded complexes. Carbon tetrachloride has a relatively positive molecular electrostatic potential surface ($\alpha = 1.4$) and so competes reasonably well for H-bond acceptor sites.[8] As a result, experimental α values are not available for functional groups that are found in many common organic solvents. Although α and β parameters can be estimated using gas phase calculations of the molecular electrostatic potential surfaces, the values are subject to a significant error.[8,15–17] We have therefore been investigating new experimental approaches to quantifying non-covalent interactions with non-polar functional groups.

In this paper, we use molecular recognition probes to characterise the H-bonding properties of non-polar organic solvents. The idea is to exploit the fact that experimental H-bond parameters, α and β, are available for a wide range of different solutes. Thus experimental measurement of association constants for a set of

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† Electronic supplementary information (ESI) available: Self association of **13** and **14** and lists of association constants. See DOI: 10.1039/b921003b

different H-bond donor (HBD) and acceptor (HBA) systems in a particular solvent should allow us to solve eqn (1) for the values of α_S and β_S. Strictly, the H-bond parameters determined using this method relate to the properties of the bulk solvent, but as explained above we assume that these are identical to the corresponding solute H-bond parameters for these molecules. For solvents that have been experimentally characterised as solutes that form H-bonded complexes in carbon tetrachloride, we can directly test the validity of this assumption.

The drawback of the approach outlined above is the large number of titration experiments that are required to collect sufficient experimental data to reliably define the values of α_S and β_S. We have therefore investigated the use of automation to implement these experiments, and here, we introduce a semi-automated NMR titration experiment. A liquid handling robot was configured to prepare NMR samples that cover the binding isotherm, the tubes were then manually transferred to the carousel of an NMR spectrometer, where the data acquisition, processing of the spectra and analysis of the data was fully automated. The quality of the results is comparable to manual titrations (see below), and although not fully automated, this approach allows collection of significant amounts of NMR titration data rapidly. An alternative source of experimental data is the literature, and in this paper, we combine data collected from the literature with experiments from our laboratory to examine the H-bond properties of a range of non-polar solvents: alkanes, perfluorocarbons, aromatic and chlorinated organic solvents.

Results

A set of sixteen HBA and HBD compounds were selected to span a range of α and β values, to minimise self-association, to provide convenient spectroscopic probes of H-bond interactions and to maximise solubility (Fig. 1). Combinations of these compounds provide access to a large number of different complexes that have a wide range of stabilities.

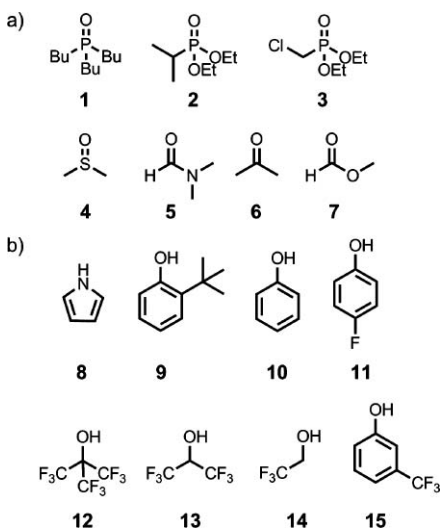

Fig. 1 (a) H-bond acceptors (HBA) and (b) H-bond donors (HBD) used in this study.

Experiments in alkane solvents

Compounds **1–3** have a strong H-bond acceptor site and no significant H-bond donors, and compounds **8–11** have a strong H-bond donor site and no significant H-bond acceptors, which should minimise problems of aggregation. Self-association was investigated in cyclohexane by ^{1}H and ^{31}P NMR dilution experiments. Although compounds **1–3** show some evidence of self-association, the association constants are low (< 5 M^{-1}), and there is no aggregation at the concentrations used in the titration experiments. Similarly, dilution experiments on compounds **8–11** in cyclohexane showed that there is no significant self-association at the concentrations used in the titration experiments.

Association constants in cyclohexane, *n*-octane and *cis*-decalin were measured for pairwise combinations of HBD and HBA compounds using ^{31}P NMR titrations. In some cases, the binding isotherms showed evidence of a second weaker binding event. These data could be fit to a 2 : 1 binding isotherm, thus allowing determination of both K_1 and K_2, but the second phase of the titration did not reach saturation. All of the data were therefore fit to an isotherm where the second association constant was fixed at 0.1 M^{-1}, which describes the second linear phase well. In cases where both K_1 and K_2 could be reliably determined, the results for K_1 were almost identical from the two fitting procedures, and the experimental association constants reported here correspond to the value of K_1 determined for the 1 : 1 complex with $K_2 =$ 0.1 M^{-1}.[14] The results are listed in Table 1. The automated NMR titrations were benchmarked using conventional manual titrations for twelve complexes, and the results are practically identical (Fig. 2). The high density and viscosity of *cis*-decalin complicates the preparation of samples using the automated liquid handler, and so the data for this solvent were collected using manual titrations only.

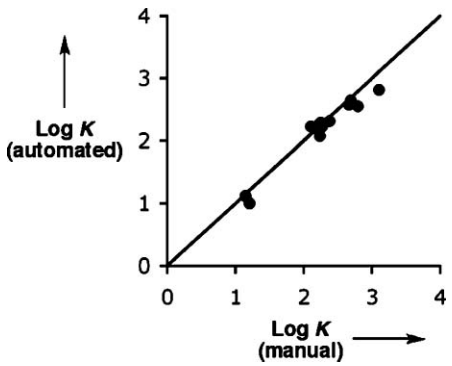

Fig. 2 Comparison of association constants (K_1) obtained using manual and automated ^{31}P NMR titrations. The line represents $y = x$.

The three different alkane solvents were chosen to investigate differences in the solvation properties of linear and cyclic alkanes. The idea that polarity and surface contacts dominate intermolecular interactions in solution suggests that there should be little difference between the solvation properties of different alkanes. However, there are remarkable differences in the physical properties of cyclic and linear alkanes, which would imply that intermolecular interactions are significantly stronger in cyclic alkane liquids.[18] Table 2 compares the boiling and critical temperatures of cyclohexane with the corresponding linear alkane, *n*-hexane,

Table 1 Association constants (K_1/M^{-1}) and free energies of complexation (ΔG/kJ mol^{-1}) for the formation of 1 : 1 complexes at 295 K from NMR titration experiments[a]

Solvent	HBA	HBD	α	β	K_{man}[b]	K_{auto}[c]	K_{exp}[d]	ΔG_{exp}
Cyclohexane	**1**	**8**	3.0	10.2	185	166	169	−12.8
	1	**9**	3.4	10.2	489	441	447	−15.3
	1	**10**	3.8	10.2	622	357	394	−14.9
	1	**11**	3.9	10.2	—	313	313	−14.4
	2	**8**	3.0	9.1	—	28	28	−8.3
	2	**9**	3.4	9.1	—	88	88	−11.2
	2	**10**	3.8	9.1	—	199	199	−13.2
	2	**11**	3.9	9.1	—	120	120	-12.0
	3	**8**	3.0	8.4	14	13	13	−6.4
	3	**9**	3.4	8.4	127	167	164	−12.7
	3	**10**	3.8	8.4	178	193	191	−13.1
	3	**11**	3.9	8.4	—	252	252	−13.8
n-Octane	**1**	**8**	3.0	10.2	172	118	145	−12.4
	1	**9**	3.4	10.2	1270	656	963	−17.0
	1	**10**	3.8	10.2	459	378	419	−15.1
	3	**8**	3.0	8.4	16	10	13	−6.3
	3	**9**	3.4	8.4	171	185	178	−13.0
	3	**10**	3.8	8.4	240	205	223	−13.5
Cis-Deacalin	**1**	**8**	3.0	10.2	46	—	46	−9.6
	1	**9**	3.4	10.2	484	—	484	−15.5
	1	**10**	3.8	10.2	145	—	145	−12.4
	3	**8**	3.0	8.4	13	—	13	−6.4
	3	**9**	3.4	8.4	153	—	153	−12.6
	3	**10**	3.8	8.4	191	—	191	−13.1
Perfluoro-*n*-hexane	**1**	**13**	4.5	10.2	4800	—	4800	−21.2
	1	**14**	3.7	10.2	9240	—	9240	−22.8
	1	**15**	4.3	10.2	59723	—	59723	−27.5
	4	**14**	3.7	8.7	372	—	372	−14.8
	4	**15**	4.3	8.7	1630	—	1630	−18.5
	5	**12**	4.9	7.7	2890	—	2890	−19.9
	5	**13**	4.5	7.7	3917	—	3917	−20.7
	5	**14**	3.7	7.7	187	—	187	−13.1
	6	**12**	4.9	5.7	482	—	482	−15.4
	6	**13**	4.5	5.7	279	—	279	−14.1
	6	**14**	3.7	5.7	40	—	40	−9.2
	6	**15**	4.3	5.7	41	—	41	−9.3
	7	**12**	4.9	4.5	82	—	82	−11.0
	7	**13**	4.5	4.5	22	—	22	−7.7
	7	**14**	3.7	4.5	4	—	4	−3.2

[a] H-bond parameters α and β obtained using eqn (2) and (4) and data from references 10 and 11. [b] K_{man} from manual titration experiments. Errors are of the order ±20%. [c] K_{auto} from automated titration experiments. Errors are of the order ±40%. [d] K_{exp} are the average of all values. Errors are of the order ±40% which corresponds to ±1 kJ mol^{-1} in ΔG_{exp}.

Table 2 Boiling (T_b) and critical (T_c) temperatures of cyclic and linear alkanes (in K)[18]

	T_b	T_c
n-Hexane	342	508
Cyclohexane	354	554
n-Decane	447	618
cis-Decalin	469	702

and *cis*-decalin with *n*-decane. The higher temperatures that are observed for cyclic alkanes are usually taken as an indication of stronger van der Waals interactions between the molecules in the liquid state.[19]

Fig. 3 shows that these differences in solvent–solvent interaction energies do not translate into differences in solvation properties. The H-bonded complexes have similar stabilities in all three alkane solvents. Eqn (1) is based on the assumption that van der Waals interactions cancel out in solution and that intermolecular interactions are dominated by the electrostatics of point contacts.[8]

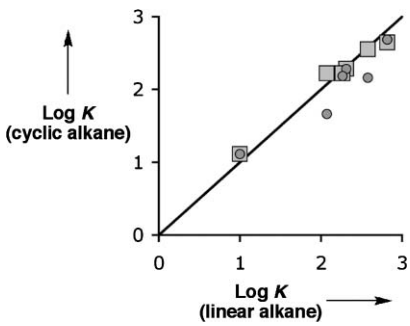

Fig. 3 Association constants (K_1) measured for six different complexes using ^{31}P NMR titrations in a linear alkane (*n*-octane) compared with the corresponding association constants measured in a cyclic alkane (cyclohexane, squares, and *cis*-decalin, circles). The line represents $y = x$.

The similarity in the behaviour of the different alkane solvents supports this basic assumption, and suggests that association

constants obtained in different alkanes can be treated collectively, because the solvent has the same functional group composition in all cases.

Experiments in perfluorocarbon solvents

The solubilities of the compounds in Fig. 1 are quite different in perfluorocarbons compared with alkanes, and in order to reach sufficiently high concentrations of guests to achieve saturation in titration experiments in perfluoro-*n*-hexane, only compounds **12–14** could be used as guests. However, **13** and **14** have H-bond acceptor sites ($\beta = 0.9$ and 2.5 respectively) in addition to the strong H-bond donor sites, and so self-association is apparent at high concentrations in perfluoro-*n*-hexane (> 10 mM). ^{1}H NMR dilution experiments were carried out for compounds **12–14** in perfluoro-*n*-hexane. Perfluoro-*tert*-butyl alcohol (**12**) shows no evidence of self-association, but both **13** and **14** give dilution isotherms that indicate significant self-association. The binding isotherms in Fig. 4(c) and (d) are sigmoidal, indicating positive cooperativity in the self-association processes.

There are two common phenomena that give rise to binding isotherms of this type: formation of cyclic oligomers that are stabilised by intramolecular binding interactions (chelate cooperativity, characterised by the effective molarity, *EM*, in Fig. 4(b)), and H-bond-induced bond polarisation which increases the H-bond strengths in oligomers relative to dimers (allosteric cooperativity, characterised by the parameter α in Fig. 4(a)).[20] The binding isotherms are very similar for the two types of cooperativity, and the data in Fig. 4 fit equally well to non-isodesmic polymerisation with $\alpha \approx 10$ (Fig. 4(a)), or to isodesmic polymerisation with a cyclic oligomer containing four, five or six monomers (Fig. 4(b)).

The presence of these aggregates affects the course of the titration experiments, and self-association of the guest must accordingly be taken into account in analysis of the titration data. For example in a titration of **14** into **4** in perfluoro-*n*-hexane, the association constant obtained from fitting with a simple 1 : 1 isotherm was 275 M^{-1}, but when the aggregation of **14** was included, the association constant was 450 M^{-1} (any of the aggregation models in Fig. 4 give the same result).

Association constants for pairwise combinations of HBD and HBA were measured in perfluoro-*n*-hexane using ^{1}H NMR titrations. Compound **15** has a chromophore that is sensitive to H-bond formation, so UV-Vis absorption spectroscopy titrations were used to evaluate the stability of complexes formed with this HBD in perfluoro-*n*-hexane. The titration data were fit to 1 : 1 binding isotherms allowing for aggregation of the guest, and the results are listed in Table 1.

Discussion

The data in Table 1 were combined with association constants from the literature to test the generality of eqn (1) and to determine appropriate values of α_s and β_s. A full list of the experimentally determined association constants used here is provided in the ESI.†[21–69] We have restricted this list to complexes for which the values of α and β for the HBD and HBA are both available from experimental measurements of α_2^H, β_2^H, pK_{HB} or pK_{HA} in carbon tetrachloride (eqn (2–5)).

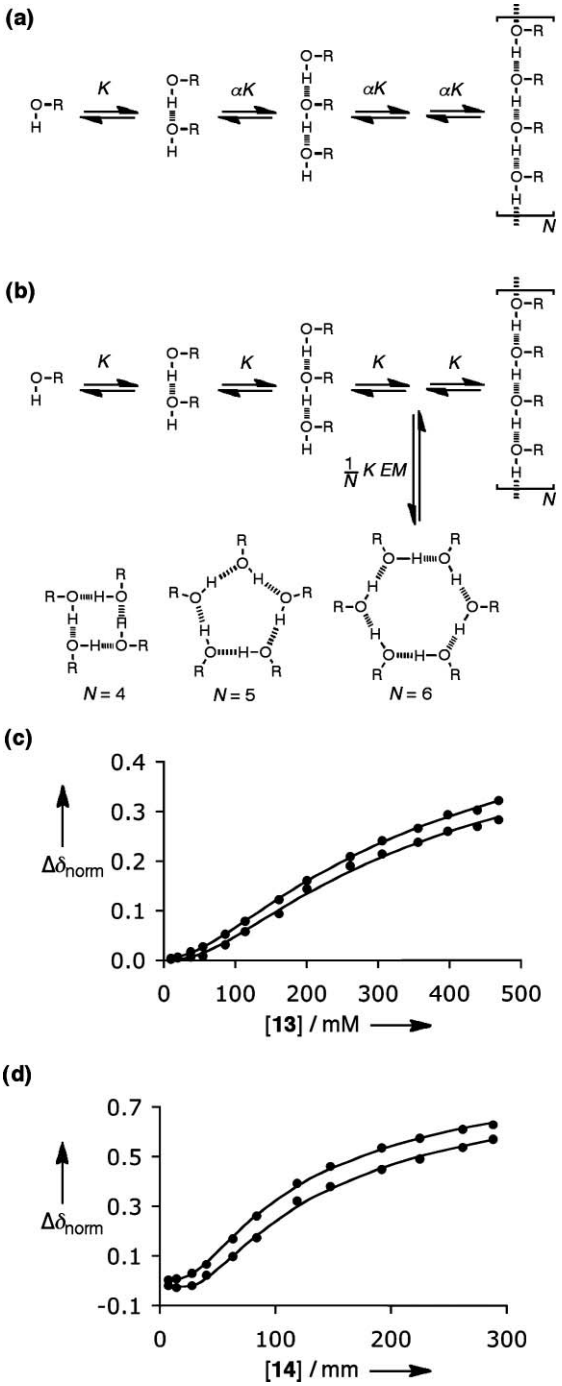

Fig. 4 Models for self-association of alcohols. (a) Non-isodesmic polymerisation to form linear H-bonded oligomers. (b) Isodesmic polymerisation with additional formation of cyclic oligomers (cyclic tetramer, pentamer or hexamer are all consistent with the experimental data). (c) ^{1}H NMR dilution data for **13**. (d) ^{1}H NMR dilution data for **14**. The best fit lines in (c) and (d) are identical for all of the models in (a) and (b). $\Delta\delta_{norm}$ is the change in chemical shift relative to the most dilute sample normalised by the extrapolated limiting change in chemical shift for each signal: the observed changes in chemical shift for the OH signals are +1 to +3 ppm, while the changes for the CH signals are < 0.1 ppm, but the two signals are plotted on similar scales as $\Delta\delta_{norm}$ (see ESI†).

Table 3 Solvent H-bond parameters, α_s and β_s, determined using eqn (1) and association constants for N different 1 : 1 complexes formed between solutes with H-bond parameters in the range α_{min} to α_{max} and β_{min} to β_{max}

solvent	α_{min}	α_{max}	β_{min}	β_{max}	N	Root mean square difference (rmsd)[a]	α_S	β_S
Alkanes	1.3	5.3	2.1	10.9	205	2.1	1.2	0.6
Perfluoro-*n*-hexane	3.7	4.9	4.5	10.2	15	2.3	1.2	0.3
Benzene	2.7	4.5	3.8	8.6	11	1.7	1.1	1.6
Chlorobenzene	2.9	3.9	4.8	10.9	10	0.7	1.4	1.1
o-Dichlorobenzene	3.9	4.9	4.8	10.9	18	0.9	1.5	0.9
Dichloromethane	2.9	3.9	2.7	10.9	15	1.9	1.7	1.5
1,2-Dichloroethane	3.9	4.1	4.8	10.9	16	1.3	1.7	1.6
1,1,1-Trichloroethane	2.2	5.3	3.3	10.1	80	1.0	1.3	1.3

[a] Root mean square difference in the free energy of complexation calculated using eqn (1) compared with experimentally determined values in kJ mol^{-1}.

$$\alpha = 4.1(\alpha_2{}^H + 0.33) \quad (2)$$

$$\alpha = 0.88(\mathrm{p}K_{HA} + 2.63) \quad (3)$$

$$\beta = 10.3(\beta_2{}^H + 0.06) \quad (4)$$

$$\beta = 2.22(\mathrm{p}K_{HB} + 1.38) \quad (5)$$

For each complex, the free energy of complexation can be estimated using eqn (1), and the difference between the experimental and calculated values was used to optimise the values of α_s and β_s for each solvent. The association constants were obtained in different laboratories using different techniques, but they span three to five orders of magnitude for all of the solvents. Fig. 5 shows the correlation between the experimental free energies of complexation and the values calculated using the best fit values of α_s and β_s. There is considerable scatter, but eqn (1) clearly describes the experimental data well with a root mean square difference between calculation and experiment (rmsd) of 1–2 kJ mol^{-1} for all eight solvents (Table 3).

Table 3 gives the best fit values of α_s and β_s, and Fig. 6 illustrates how well these values are constrained by the experimental data. For example, the values for 1,1,1-trichloroethane are rather well-defined with a clear minimum in the rmsd at $\alpha_s = 1.3$, $\beta_s = 1.3$ (Fig. 6(h)). In contrast, the experimental data for dichloromethane can be equally well described by a range of different α_s, β_s combinations within the window $1.3 < \alpha_s < 2.0$, $0.5 < \beta_s < 2.5$ (Fig. 6(f)). This reflects both the number of experimental measurements, N, that are available and the range of HBD properties (α_{min} to α_{max}) and HBA properties (β_{min} to β_{max}) that have been studied (Table 3).

For some of the solvents in Table 3, H-bond parameters have been measured experimentally using the formation of 1 : 1 H-bonded complexes in carbon tetrachloride, *i.e.* using the compounds as a solute. Table 4 compares the values of α and β obtained when the compound is the solute with the values of α_s and β_s obtained when the compound is the solvent. There is good agreement suggesting that the assumptions underpinning eqn (1) are valid, and there is no difference between solvent and solute H-bond parameters. We can also estimate the H-bond parameters

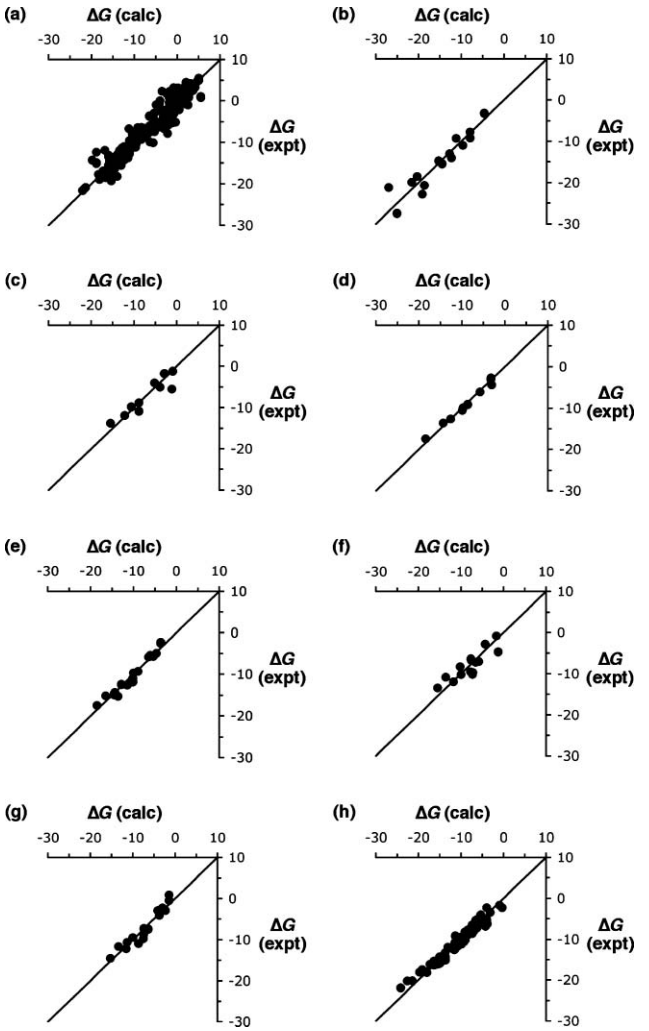

Fig. 5 Comparison of the free energy of complexation for H-bonded complexes calculated using eqn (1) and the best fit values for α_s and β_s in Table 3, ΔG(calc), with the corresponding experimental data, ΔG(expt) in (a) alkanes (*n*-hexane, *n*-heptane, *n*-octane, *i*-octane, cyclohexane, *cis*-decalin) (b) perfluoro-*n*-hexane (c) benzene (d) chlorobenzene (e) *o*-dichlorobenzene (f) dichloromethane (g) 1,2-dichloroethane (h) 1,1,1-trichloroethane. The straight lines represent $y = x$.

using the calculated maxima and minima on AM1 molecular electrostatic potential (MEP) surface (E_{max} and E_{min}) and eqn (6) and 7.

$$\alpha = \frac{E_{max}}{52 \text{ kJ mol}^{-1}} \quad (6)$$

$$\beta = \frac{-E_{min}}{52 \text{ kJ mol}^{-1}} \quad (7)$$

Table 4 shows that the calculated MEP values also agree reasonably well with the experimental H-bond parameters. However, there are deviations in the α_s values for alkanes, and to a lesser extent for perfluorocarbons. The calculated parameters underestimate the experimental polarity of these very non-polar solvents, and it is clear that alkanes, in particular, are much better solvents than the MEP calculation suggests. There are a number of potential explanations for this discrepancy:

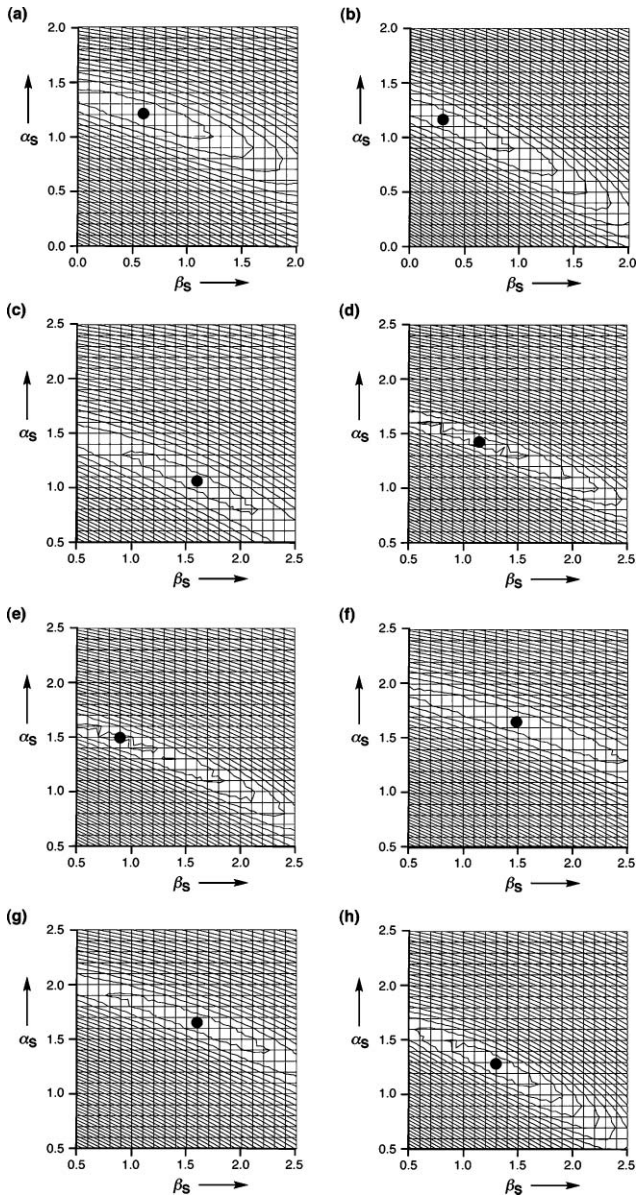

Fig. 6 Root mean square difference (rmsd) between the free energy of complexation for H-bonded complexes calculated using eqn (1) and the corresponding experimental values plotted as a function of the solvent H-bond parameters, α_s and β_s, in (a) alkanes (*n*-hexane, *n*-heptane, *n*-octane, *i*-octane, cyclohexane, *cis*-decalin) (b) perfluoro-*n*-hexane (c) benzene (d) chlorobenzene (e) *o*-dichlorobenzene (f) dichloromethane (g) 1,2-dichloroethane (h) 1,1,1-trichloroethane. The contour spacing is 0.2 kJ mol^{-1}. The solvent parameters that minimise the rmsd are indicated as black circles.

- there is a large error margin in the calculated MEP parameters;
- there is a very high concentration of CH donors in an alkane solvent compared with the other solvents studied here, and this perturbs the solvation equilibria;
- there is a residual van der Waals interaction that only becomes important when electrostatic interactions are too weak to perturb the solvation equilibria.

It is difficult to distinguish these possibilities, but from an operational point of view, the experimentally determined solvent parameters in Table 4 allow the estimation of H-bond strengths in non-polar organic solvents with some confidence.

Table 4 H-bond parameters for non-polar solvents

	Experiment as solvent		Experiment as solute[a]		Calculated from MEP	
Solvent	α_S	β_S	α	β	α	β
Alkanes	1.2	0.6	—	—	0.4	0.3
Perfluoro-*n*-hexane	1.2	0.3	—	—	0.7	0.7
Benzene	1.1	1.6	—	2.1	1.0	1.9
Chlorobenzene	1.4	1.1	—	1.8	1.3	1.4
o-Dichlorobenzene	1.5	0.9	—	—	1.5	1.3[b]
Dichloromethane	1.7	1.5	1.9	1.1, 2.0[c]	2.0	1.6
1,2-Dichloroethane	1.7	1.6	1.7	2.4	1.3	1.3
1,1,1-Trichloroethane	1.3	1.3	1.4	1.5	1.5	1.4

[a] H-bond parameters α and β obtained using eqn (2–5) and data from references 9, 10, 11 and 70. This data is not available for compounds that are not sufficiently polar to form H-bonded complexes in carbon tetrachloride. [b] This value comes from the exposed π-face of the chlorine atoms. The minimum MEP on the van der Waals surface gives $\beta = 2.1$, but this is for a site located in a crevice between the chlorine atoms that is not sterically accessible. [c] Two different values in the literature.[10,70]

Conclusions

This paper introduces a new approach to characterisation of the H-bond properties of solvents. We assume that the functional group H-bond parameters α or β are a universal property of a functional group in a molecule and can be used interchangeably as α_s or β_s for a solvent molecule, or as α or β for a solute in eqn (1). Thus the measurement of 1 : 1 association constants for H-bonded complexes between solutes with a range of α and β parameters in a particular solvent allows determination of the values of α_s and β_s for that solvent. The drawback of this approach is that a large amount of experimental titration data is required to reliably determine α_s or β_s, and so we have introduced a semi-automated NMR titration protocol that yields results that are comparable to those obtained with more labour intensive manual experiments.

We have applied these methods to characterise the H-bond properties of very non-polar functional groups that are difficult to study by conventional methods, but are common to most organic solvents. For compounds where the solute H-bond properties have been measured in carbon tetrachloride solution, we find that the solvent H-bond parameters measured here are practically identical. This demonstrates that the solvent competition model embodied in eqn (1) is a valid approach to quantifying solvent effects on intermolecular interactions. In essence, there is no intrinsic difference between a solvent and a solute molecule, and complexation equilibria simply involve exchange of functional group interactions between the molecules with minimal effect of the surrounding bulk solvent. For compounds that are not sufficiently polar to observe H-bond interactions in carbon tetrachloride solution, the approach presented here provides new experimental H-bond parameters for use in eqn (1). These new experimental parameters compare reasonably well with the values estimated from calculated MEP surfaces. However, the very non-polar solvents, alkanes and perfluorocarbons, appear to be better solvents than expected based on the calculations. In these cases, the α_s parameter is significantly larger than predicted by

calculation. This result may reflect the importance of van der Waals interactions that are ignored in our approach. However, the solvation properties of cyclic and linear alkanes, which have very different van der Waals interactions, are indistinguishable, so the origin of this effect remains an open question.

Experimental

Automated NMR titrations

For each titration, 12 NMR tubes containing varying amounts of guest and host were prepared using an automated liquid handler. Host stock solutions were prepared at a known concentration according to the stability of the complex ([H] ≈ $1/K$). Guest stock solutions were prepared by dissolving the guest in a sample of the host stock solution. NMR samples were automatically prepared by adding appropriate volumes of the host and guest stock solutions. External capillaries containing a 25 mM solution of methylene diphosphonic acid in D_2O to provide a ^{31}P reference signal ($\delta = 17.98$ ppm) and a deuterium lock signal were added, and the samples were transferred to the carousel of an automated Bruker AMX400 NMR spectrometer. An ICON-NMR routine was used to automatically record the ^{31}P NMR spectra of each sample and export the chemical shifts of the two ^{31}P signals in each sample as a single excel spreadsheet. The data were then fit to a 1 : 1 binding isotherm allowing for a second binding interaction ($K_2 = 0.1$ M^{-1}) using purpose-written software. This process optimised the association constant, and the bound and free chemical shifts to obtain the best fit to the experimental data. Since the NMR carousel can hold 60 samples, it is possible to run five titrations at once, which takes about 4 h in total.

Manual NMR titrations

Host solutions were prepared at a known concentration, depending on the stability of the complex ([H] ≈ $1/K$). Guest stock solutions were prepared by dissolving the guest in a sample of the host stock solution, so that there was no dilution of the host during the titration. On addition of aliquots of the guest solution, the NMR tube was thoroughly shaken to mix the two solutions. The ^{31}P NMR spectra were recorded on a Bruker AMX400 spectrometer. The observed changes in chemical shift of the host signals as a function of guest concentration were fit to a 1 : 1 binding isotherm allowing for a second binding interaction ($K_2 = 0.1$ M^{-1}) using purpose-written software, which yields the association constant, the bound chemical shift and the free chemical shift.

UV-Vis absorption titrations

Association constants were determined using standard UV-Vis titration protocols. Host solutions were prepared at known concentration in perfluoro-*n*-hexane. Guest solutions were prepared by dissolving the guest in a sample of the host stock solution, so that there was no dilution of the host during the titration. On addition of successive aliquots of the guest solution into the cell, the UV-Vis spectrum was recorded. Changes in absorbance were fit to a 1 : 1 binding isotherm allowing for a second binding interaction ($K_2 = 0.1$ M^{-1}) using purpose-written software, which yields the association constant and the absorbances for the free and bound states.

Data analysis

The formation of 1 : 1 complexes between a HBD and a HBA were analysed using eqn (8) and 9.

$$[\text{HBA}\cdot\text{HBD}] = K_1[\text{HBA}][\text{HBD}] \quad (8)$$

$$[\text{HBA}\cdot(\text{HBD})_2] = K_2[\text{HBA}][\text{HBD}]^2 \quad (9)$$

where [HBA·HBD] is the concentration of the 1 : 1 complex, [HBA·$(HBD)_2$] is the concentration of the 2 : 1 complex and [HBA] and [HBD] are the concentrations of the unbound species.

The linear oligomerisation isotherm for a HBD (or HBA) is described by eqn (10) and 11.[20]

$$[\text{bound oligomeric HBD}] = \frac{K[\text{HBD}]^2}{\alpha(1 - K[\text{HBD}])^2} \quad (10)$$

$$[\text{unbound oligomeric HBD}] = \frac{K[\text{HBD}]^2}{\alpha(1 - K[\text{HBD}])} \quad (11)$$

where [bound oligomeric HBD] is the concentration of HBD bound in linear oligomers, [unbound oligomeric HBD] is the concentration of unbound HBD end group in linear oligomers, [HBD] is the concentration of the monomeric HBD, K is the self-association constant, and α is the allosteric cooperativity parameters defined in Fig. 4(a). For isodesmic polymerisation, $\alpha = 1$, and for non-isodesmic polymerisation, $\alpha \neq 1$.

The formation of cyclic oligomers of a HBD (or HBA) is described by eqn (12).[20]

$$[c - \text{HBD}_N] = \frac{1}{N} K^N EM[\text{HBD}]^N \quad (12)$$

where [c-HBD_N] is the concentration of the cyclic N-mer and EM is the effective molarity for the intramolecular cyclisation interaction, as defined in Fig. 4(b). In cases where linear and cyclic species co-exist, it is possible to determine both K and EM in a titration experiment, but if the cyclic complex dominates, then it is only possible to determine the value of K(global) = $(1/N)$ K^N EM.

The dilution and titration data were analysed by including all of the relevant equilibria above and solving the simultaneous equations using the Solver routine in Excel to obtain best fit values for the association constants, and the bound and free spectroscopic properties. Where oligomerisation was important in the titration experiments, *i.e.* for **13** and **14**, the results of separate dilution experiments were used to independently determine the self-association parameters in order to minimise the number of variables used to fit the titration data.

Semi-empirical calculations

The Spartan software package was used to build molecular structures, which were then optimised using AM1, and the maxima and minima in the electrostatic potential calculated on the 0.002 Bohr/Å^3 isodensity surface were used to estimate H-bond parameters using eqn (6) and 7.[71]

Acknowledgements

We thank the EPSRC for funding.

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