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The affinity of some Lewis bases for Hexafluoroisopropanol as a reference Lewis acid : an ITC/DFT study.

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Abstract: To figure out the possible role of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as well as to provide reference thermochemical data in solution, the formation of Lewis acid-base complexes between HFIP (Lewis acid) and a series of 8 different Lewis bases (3 sulfoxides, 3 Nsp² pyridine derivatives, 1 aromatic amine, 1 cyclic aliphatic ether) was examined by Isothermal Titration Calorimetry (ITC) experiments and static Density Functional Theory augmented with Dispersion (DFT-D) calculations. Measured ITC association enthalpy values ΔH_a spanned -9.3 kcal/mol to -14 kcal/mol. Computations including a PCM implicit solvation model produced similar exothermicity of association of all studied systems compared to the ITC data with ΔH_a values ranging -8.5 – -12.7 kcal/mol. An additional set of calculations combining implicit and explicit solvation by chlorobenzene of the reactants, pointed out the relatively low interference of the solvent with the HFIP-base complexation, which main effect is to slightly enhance the Gibbs energy of the HFIP-Lewis base association. It is speculated that the interactions of bulk HFIP with Lewis bases therefore may significantly intervene in catalytic processes not only via the dynamic microstructuration of the medium but also more explicitly by affecting bonds' polarization at the Lewis bases.

Introduction

Recently, due to its acidic and polar features,^[1] strong hydrogen bonding capabilities,^[1b-c, 2] high ionizing and stabilizing ability,^[1c, 2c] as well as low boiling point, low viscosity, and recyclability,^[3] 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP, **1**) was found to be an exceptional medium,^[4] either as solvent or co-solvent, that allows many reactions to occur.^[2a, 3-5] However, the exact role and mode of action of HFIP in various chemical transformations still remains elusive. It is known that aqueous alcohol mixture, especially aqueous mixture of HFIP, has a stabilizing effect on α -helical structure of proteins and peptides^[6] as well as on their

separation.^[7] Furthermore molecular dynamics studies carried out by Kirchner et al. strongly suggest that bulk HFIP should be seen as a microstructured heterogenous solvent with polar and apolar domains that can adapt and dynamically rearrange depending on the solutes.^[8]

It has been found that HFIP is useful in the generation of intermediate conformation of proteins^[9] within investigations of Alzheimer and prion diseases^[10] as well as in other applications within biochemical researches.^[11] Even though there have been many attempts to reveal molecular structure and properties of water-HFIP mixture^[12] mainly suggesting micellar aggregates with fluoroalkyl groups located in micelle, detailed structure has remained unexplored. It has been reported that the water-HFIP mixtures existing within microheterogeneities of HFIP and water clusters depend on the mole fraction of HFIP.^[8, 12b, 13]

Despite many reports dealing with water/HFIP complexes, little has been published on other molecular complexes of HFIP as well as on thermochemistry of the formation of such complexes.^[14] In a rare example given by Maiti *et al.* and McElroy *et al.*,^[14] among other characteristics, the enthalpies of H-bond formation within complexes of HFIP and tertiary amines and enthalpies of mixtures with acetonitrile, ethyl acetate, acetone, diethylether, *N,N*-dimethylacetamide, hexamethylphosphoramide and triethylamine have been reported. Within this study the affinity of various Lewis bases to HFIP (see Scheme 1), are investigated experimentally by means of ITC as well as theoretically using static DFT-D calculations. Consequently, the present study had two main purposes: to provide an amount of experimental thermochemical data in solution and to shed light on the possible role of HFIP in chemical transformations.

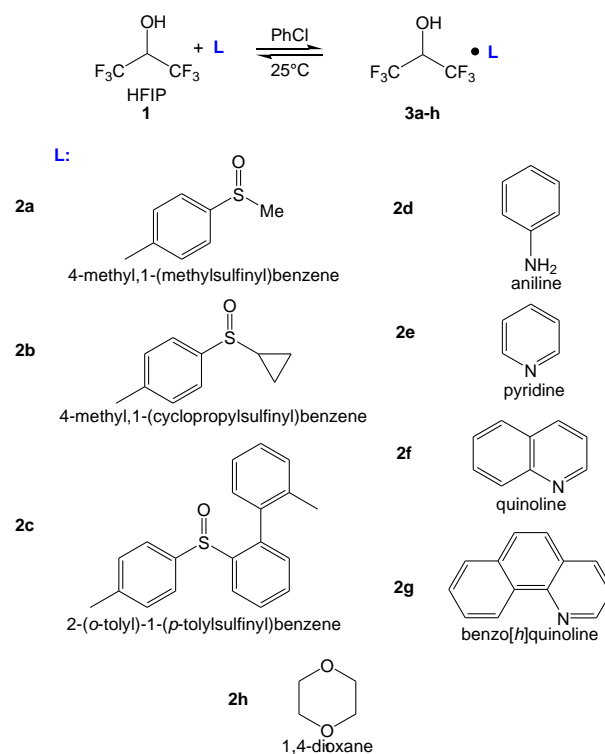
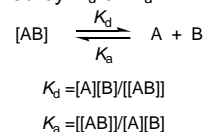
Results and Discussion

ITC experiments. To find proper conditions for ITC measurements two approaches were employed. The first tests used either HFIP (**1**, Scheme 1) as reagent in the sample cell, while substrates **2a-h**, Scheme 1) were injected through the ITC syringe, or the reverse. However, whatever the order and concentrations of the substrates, no exploitable ITC heat response was obtained (i.e. no possibility to fit the curve). Some examples of these results are summarized in Figure SI 1 (see Supporting Information). Moreover, it was noticed that the heat released upon the titration experiments was relatively low (ca. 2-3 kcal/mol).

An alternative approach consisted of making a concentrated molar 1:1 mixture of HFIP (**1**) and Lewis base (**2a-h**) in pure chlorobenzene, containing amounts of molecular complex [**1**•**2**]. Such solutions were afterwards placed in the servo-controlled ITC syringe and sequentially injected into the ITC sample cell filled with pure chlorobenzene to measure the heat change in the ITC instrument caused by the possible disruption of the molecular assembly by dilution of its concentrated solution. Concentrations of these solutions that generated reasonable ITC thermograms were found to be in the range of 80-130 mmol/L. Note that the obtained heats resulted from two main processes: a) the dissociation of the complex (**3a-h**), which must be an endothermic process; b) the solvation of the substrates by pure chlorobenzene. Separately, by performing blank experiments (dilution of each substrate separately under the same condition), it was found that the heat of dilution of separate substrates is mostly negligible (around 100 μ J) compared to the heat of dissociation (a couple of mJ). For the sake of consistency, dilution heats were subtracted from the measured ITC heat during its treatment by the NanoITC Analyze software.

As mentioned above, endothermic dissociation enthalpy values (ΔH_d) bear a positive sign by convention. Hence, in Table 1 the corresponding association enthalpies (ΔH_a) are basically of the opposite sign. Figure 1 displays the ITC thermogram of dissociation of the **3a**, as an example of the shape of ITC thermograms, since all herein studied molecular complexes exhibit very similar ITC thermograms (see Figure SI 2-8). The

dissociation process is related to the displacement of an equilibrium characterized by K_d or K_a :



Scheme 1 Schematic representation of the investigated reactions within the study of the affinity of various Lewis bases (**2a-h**) to HFIP (**1**) and formulas of Lewis bases used throughout ITC experiments and static DFT-D calculations.

Table 1. Thermodynamic data obtained by ITC experiments and DFT (PBE-D3-BJ/def2-TZVP) calculations of the affinity of the Lewis bases (**2a-h**) to HFIP (**1**) (Scheme 1). All the values are in kcal mol⁻¹ and were acquired and computed at T= 298.15 K.

Base	Thermodynamic data from model fitting ^[a]		DFT with implicit solvation ^[b]	
	$\Delta H_{a[1/2]}(\text{fit})$	$\Delta G_{a[1/2]}(\text{fit})$	$\Delta H_{a[1/2]}$	$\Delta G_{a[1/2]}$
2a	-12.9 \pm 0.8	-3.2 \pm 0.6	-10.2	0.0
2b	-10.1 \pm 0.6	-2.9 \pm 0.5	-10.0	0.2
2c	-10.1 \pm 0.4	-2.7 \pm 0.4	-10.9	-0.3
2d	-10	n.a.	-9.4	0.6
2e	-14 \pm 1	-3.2 \pm 0.8	-11.9	-3.2
2f	-11.8 \pm 0.3	-1.9 \pm 0.4	-12.7	-2.4
2g	-12.3 \pm 0.8	-1.4 \pm 0.3	-11.4	-0.2
2h	-9.3 \pm 0.3	-1.4 \pm 0.2	-8.5	0.8

[a] values were obtained by the whole thermogram (ITC trace) with Cooper's model for dimer dissociation.^[15] [b] ΔH_a , and ΔG_a are data on the association of HFIP (**1**) and Lewis bases (**2a-h**), forming adducts **3a-h** (by OH...O bonding at the sulfoxide) (Scheme 1, Figure 2).

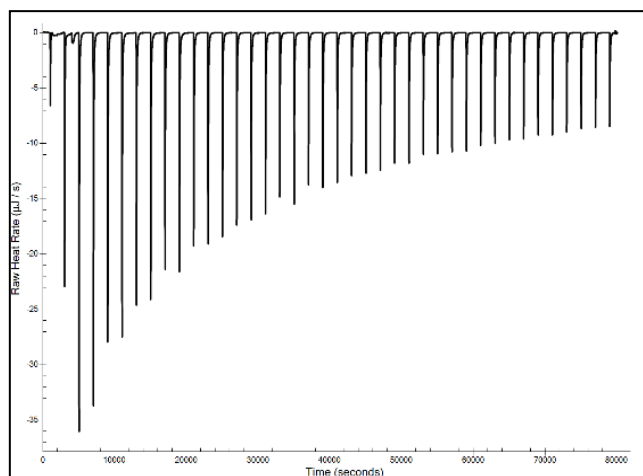


Figure 1 ITC thermogram of the dilution of a concentrated solution of **1** and **2a** (syringe, $c = 82.44$ mM) in chlorobenzene. The titration was performed at 25°C through 39 sequential additions (of 2.06 μL each). Time between two consecutive injections was 2000 s. Heat released is expressed in $\mu\text{J/s}$ versus time in s.

Accordingly, the shape of the ITC thermogram of the dissociation of the complex **3a** shown in Figure 1 can be rationally explained. At the beginning of the sequential titrations, the endothermic heat response due to the dissociation of the complex is the highest. As new portions of the complex are being injected, the equilibrium mixture simultaneously adapts itself accordingly to the equilibrium constant (either K_d or K_a) and relaxes to meet the new conditions, which leads to a steady decrease of the relative heat change per injection.

Table 1 and Table SI 1 contain the experimental thermodynamic data extracted by applying Cooper's^[15] dimer dissociation ITC curve-fitting model applied to HFIP-**2a-h** molecular complexes. Based on the data of association of sulfoxides (**2a-c**) with HFIP (**1**) in PhCl, it seems that there is a slight discriminatory influence of the second substituent on sulfur atom on the total interaction enthalpies. Namely, if methyl group is the substituent (**2a**), the association enthalpy ($\Delta H_{a[1/2]}(\text{fit})$) is the highest, around -13 kcal/mol. That might be accompanied with small bulkiness of the methyl group giving a possibility to the OH group to properly interact with the oxygen or sulfur atom. As the bulkiness of the substituent increases, the association enthalpy decreases. The same $\Delta H_{a[1/2]}(\text{fit})$ value (around -10 kcal/mol) for **2b** and **2c** is probably caused by two opposite effects: the substituent bulkiness and the strength of interaction of aliphatic hydrogen atom against aromatic hydrogen atom with a fluorine atom.

The $\Delta H_{a[1/2]}(\text{fit})$ value of an association of aniline (**2d**) with HFIP (**1**) is the lowest (around -10 kcal/mol), most probably due to its the lowest basicity among the series of investigated amines (**2d-g**). Structural differences between the three other aromatic amines could rationally explain slight differences in their $\Delta H_{a[1/2]}(\text{fit})$ values. Namely, in the case of pyridine (**2e**), which exhibits the highest association tendency towards HFIP (with $\Delta H_{a[1/2]}(\text{fit})$ around -14 kcal/mol) its moderate basicity and molecular simplicity might allow preferable orientation of HFIP resulting in relatively strong OH-N hydrogen bond. Although quinoline (**2f**), compared to benzo[h]quinoline (**2g**) possesses one aromatic ring less, it seems that the number of the

condensed aromatic rings has no influence on the $\Delta H_{a[1/2]}(\text{fit})$ value, as their $\Delta H_{a[1/2]}(\text{fit})$ values are ca -12 kcal/mol.

Considering the $\Delta H_{a[1/2]}(\text{fit})$ of dioxane (**2h**), that is -9.3 kcal/mol one could conclude that the relative flexibility of heteroaliphatic ring has no dramatic influence on interactions with HFIP.

Static DFT-D calculations. Static DFT-D calculations were performed in order to estimate the association energies as well as to survey the influence of the solvent on association of **1** and **2a-h** in the formation of adducts **3a-h** (Scheme 1) considering that in dilute solution the possible microstructuration of HFIP^[6] is arguably improbable if best inexistent. However, the possible interference of the solvent remained a possible issue that deserved a full theoretical treatment by considering both implicit and explicit solvation.

To evaluate the values of association enthalpies by theory, we used two alternative routes to model solvation effects, one with implicit and one with a combination of implicit and explicit solvation. First, we calculated interaction energies ($\Delta E_{a[1/2]}$) and $\Delta H_{a[1/2]}$, $\Delta G_{a[1/2]}$, $\Delta S_{a[1/2]}$ values corresponding to the optimized geometries of adducts **3a-h** (Scheme 1, Figure 2, Table 1, Table SI 1) using a standard implicit solvation model (Polarizable Continuum Model, abbr. PCM).

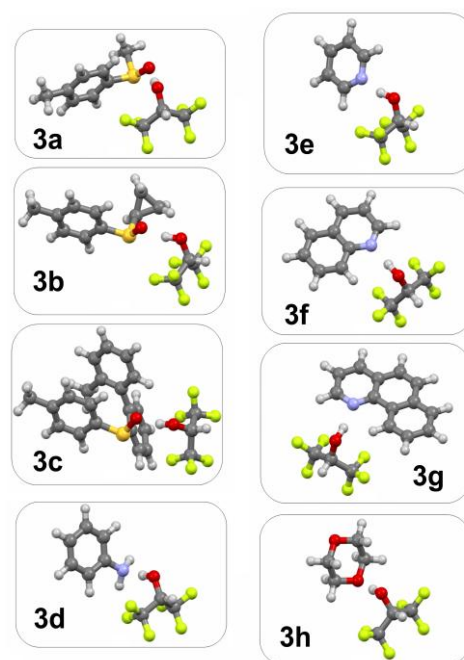


Figure 2 Graphic representations of optimized geometries of the investigated systems (**3a-h**, Scheme 1) at PBE-D3(BJ)/def2-TZVP level of theory in chlorobenzene solution (PCM) phase. S: orange; O: red; N: violet; F: yellowish; Br: brown; C: grey; H: white. Corresponding thermodynamic parameters are shown in Table 1. For **3a-c** only the more stable OH...O situations are depicted.

Worthy to note, in the case of **2a-c**, the interaction of HFIP with both S and O centres was considered (see Figure 3 for the two topomers of **3b**). It is indeed known that sulfoxides express a Pearson's soft base character at S and a hard base character at O, which explains the propensity of the former to bind metal ions and the latter to be protonated.^[16] DFT calculations carried out in the gas phase (Table SI 2 and Figure SI 9) and with implicit solvation produced consistently association enthalpies by 5-6

kcal/mol lower for the OH...S interactions (not shown here) as compared to the OH...O situation depicted in Figure 2. NCI plots (Figure 3) also confirmed the existence of H-bonds materialized by attractive red-colored isosurface for the two topomers. Further determination of the intrinsic interaction energy from Ziegler's Energy Decomposition Analysis^[17] between so-called prepared fragments **2a-c** and **1** in **3a-c** in gas phase geometries of both OH...S and OH...O situations indicated clearly that the former H-bonding situation with the sulphur centre was less cohesive with the oxygen of the sulfoxide owing to the large H-to-S distance in the OH...S topomer. We therefore essentially considered the OH...O situations for **3a-c**, the enthalpies of association (formation) of which are listed in Table 1.

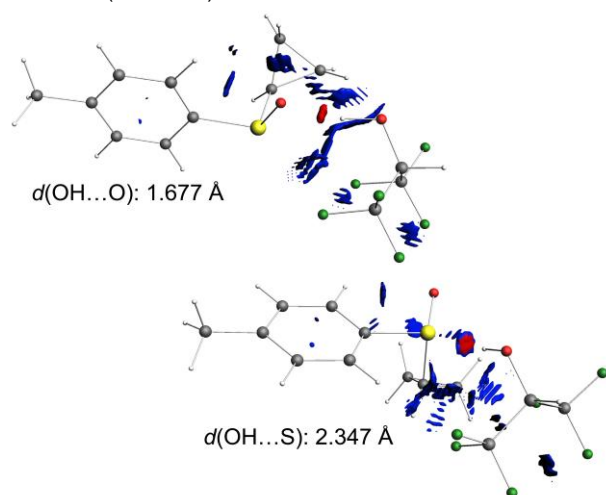


Figure 3 ADFview of noncovalent interaction (NCI) plots for the $(\text{CF}_3)_2\text{CHOH}\cdots\text{O}_{2b}$ (top) and $(\text{CF}_3)_2\text{CHOH}\cdots\text{S}_{2b}$ (bottom) topomers of molecular complex **3b** showing attractive red colored attractive NCI domains materializing H-bonding between the HFIP fragment and **2b**. Intrinsic interaction energies show that the strongest cohesion arises from the $(\text{CF}_3)_2\text{CHOH}\cdots\text{O}_{2b}$ topomer. NCIs are materialized by reduced density gradient isosurfaces (cut-off value $s = 0.02$ a.u., $\rho = 0.05$ a.u.) colored according to the sign of the signed density $\lambda_2\rho$; isosurfaces are colored in red and blue for attractive and repulsive (or non-bonded) NCI respectively.

The calculated association enthalpies $\Delta H_{a[1/2]}$ values (ca. -8.5 – -12.7 kcal/mol, Table 1) show a trend similar to the experimental data ($\Delta H_a(\text{fit})$ values, ca. -9.3 kcal/mol – -14 kcal/mol, Table 1). The calculated association enthalpies are consistent within **3a-h**. Namely, the calculated $\Delta H_{a[1/2]}$ values for the sulfoxides (**2a-c**) are span ca. -10 kcal/mol – -11 kcal/mol (Table 1) which is in good accordance with experimental $\Delta H_{a[1/2]}(\text{fit})$ values (Table 1), with only exception in the $\Delta H_{a[1/2]}(\text{fit})$ for **2a** (ca -13 kcal/mol). In case of amines (**2d-g**) the calculated $\Delta H_{a[1/2]}$ values ranging -9.4 kcal/mol – -12.7 kcal/mol (Table 1) show similar trend as the experimental $\Delta H_{a[1/2]}(\text{fit})$ values (Table 1) with only exception in the $\Delta H_{a[1/2]}(\text{fit})$ for **2e** (ca -14 kcal/mol). In the case of dioxane (**2h**), the $\Delta H_{a[1/2]}$ value of ca. -8.5 kcal/mol (Table 1) is in good agreement with the corresponding experimental $\Delta H_{a[1/2]}(\text{fit})$ value (ca. -9.3 kcal/mol, Table 1). This relative agreement between the experimental and calculated $\Delta H_{a[1/2]}$ values is symptomatic of a rather low impact of explicit solvation. However, solvation interactions of chlorobenzene with the reactants should not be systematically excluded nor considered as negligible. A competition between solvent attractive (non-covalent) interactions and the interactions of reactants may exist and

corrupt the experimental data due to unaccounted weak interactions such as halogen bond for instance. To gauge the extent of explicit solvation, we performed an additional set of calculations. We calculated interaction thermodynamic parameters ($\Delta H_{a[4/1]}$, $\Delta G_{a[4/1]}$, $\Delta S_{a[4/1]}$, $\Delta E_{a[4/1]}$, $\Delta H_{a[4/2]}$, $\Delta G_{a[4/2]}$, $\Delta S_{a[4/2]}$, $\Delta E_{a[4/2]}$, $\Delta H_{a[4/3]}$, $\Delta G_{a[4/3]}$, $\Delta S_{a[4/3]}$ and $\Delta E_{a[4/3]}$) of the solvent (**4**) interacting explicitly with HFIP (**1**), Lewis bases (**2a-h**) and reaction products (**3a-h**) using optimized geometries of chlorobenzene's adducts (**4•1**, **4•2a-h** and **4•3a-h**) (Table SI 1, Figure SI 10-11).

By calculating the thermodynamic parameters ($\Delta H_{a[4/1]}$, $\Delta G_{a[4/1]}$, $\Delta H_{a[4/2]}$ and $\Delta G_{a[4/2]}$) (Scheme SI 1, Table SI 1) of the association process between the reactants (**1**, **2a-h**) and chlorobenzene (**4**) (with PhCl as the implicit solvent) approximate corrective terms for an explicit solvation were determined. It can be noticed that the enthalpy contribution of the explicit solvation of **1** (Figure SI 10, Scheme SI 1) is significant, as $\Delta H_{a[4/1]}$ value is -3.7 kcal/mol (Table SI 1), while $\Delta H_{a[4/2]}$ values of the adducts **4/2a-h** (Figure SI 10, Scheme SI 1) range from ca. -2.8 kcal/mol up to -5.5 kcal/mol (Table SI 1). The calculated corrected interaction enthalpy values of $\Delta\Delta H_{a[1/2]}$ ranged from ca. -1.6 kcal/mol to ca. -5.3 kcal/mol (Table SI 1). The corrected Gibbs enthalpy ($\Delta\Delta G_{a[1/2]}$) values are highly negative (ranging from ca. -6.8 kcal/mol to ca. -10.6 kcal/mol, Table SI 1) suggesting an even more spontaneous association of **1** and **2a-h** in chlorobenzene solutions.

However, after analysis of the optimized geometries of the chlorobenzene's assemblies (**4/2a-h** and **4/1**, Figure SI 10), it can be concluded that the herein used assumption of full displacement of one chlorobenzene molecule during the association process between **1** and **2a-h** is not totally reliable. Namely, chlorobenzene interacting with **2a-h** (by π -stacking interactions) does not significantly cover the reactive center(s) of **2a-h** and therefore does not interrupt their subsequent interactions with HFIP. Since full displacement of chlorobenzene molecule should not be an expected scenario within these systems (**4/2a-h**), another corrective scheme including the explicit solvation of the reaction products (**4/3a-h**) was applied (Scheme SI 1). The calculated corrected thermodynamic values in that way ($-5.2 < \Delta\Delta H_{a[1/2]} < -10.3$ kcal/mol and $-2.5 < \Delta\Delta G_{a[1/2]} < -5.7$ kcal/mol, Table SI 1) are closer to the corresponding experimental values ($\Delta H_{a[1/2]}(\text{fit})$ and $\Delta G_{a[1/2]}(\text{fit})$ values, Table 1), than the former corrected values ($\Delta\Delta H_{a[1/2]}$ and $\Delta\Delta G_{a[1/2]}$ values, Table SI 1), however not as close as the calculated thermodynamic values assuming only the implicit solvation model ($\Delta H_{a[1/2]}$ and $\Delta G_{a[1/2]}$ values, Table 1).

These data confirm that the treatment of solvation based on implicit solvation with standard parameters used in the calculations is mostly sufficient when the solvent does not establish persistent interactions with reactants for which a treatment of the explicit solvation is in principle recommended to recover some consistency with experimental data. In the case of PhCl it is difficult to judge the impact of the static model of explicit interaction. However even of low impact, explicit solvent interaction should seemingly not be detrimental to the interaction between **1** and **2a-h** by virtue of the negative corrected values of Gibbs energy variation ($\Delta\Delta G_{a[1/2]}$ or $-\Delta\Delta G_{a[1/2]}$, Table SI 1) which tend to make the interaction more "cohesive".

Considering only the pure propensity of association of **1** and **2a-h** from the calculated Gibbs enthalpies of association ($\Delta G_{a[1/2]}$, Table 1), that are from slightly positive (0.8 kcal/mol) to

moderately negative (-3.2 kcal/mol), one could conclude that all Lewis bases (**2a-h**) would, more or less, spontaneously interact with HFIP (**1**). This information accompanied with significant association enthalpies ($-8.5 < \Delta H_{a[1/2]} < -12.7$ kcal/mol, Table 1) might have a significant influence on the polarization of bonds within a given base and impact its chemical reactivity. This study shows that accounting for such interactions with HFIP in computing energy reaction profiles is way justified even though it is obvious that reproducing faithfully the physical effects of a dynamic microstructured solvent displaying polar and apolar domains by a static DFT approach still remains illusory.

Conclusion

The affinities of various Lewis bases (sulfoxides (**2a-c**), amines (**2d-g**) and dioxane (**2h**), Scheme 1) to HFIP (**1**, Scheme 1) were estimated experimentally (by ITC) and theoretically (by static DFT/D3). ITC experiments were carried out assuming a dissociation of the pair formed between HFIP and Lewis base. The ITC results showed relatively moderate non-covalent interactions ($\Delta H_{a[1/2]}(\text{fit})$ span -9 kcal/mol – -14 kcal/mol) within the studied systems. DFT calculations assuming implicit solvation produced $\Delta H_{a[1/2]}$ values ranging from ca. -8.5 kcal/mol to -12.7 kcal/mol of similar magnitude than the experimental ones. It is shown, by assuming explicit interactions of chlorobenzene with the solutes that it may interact with HFIP as well as with all studied Lewis bases, but with a rather unfavorable Gibbs energy variation though. In this work, an experimental set of thermochemical data pertaining to affinity of several Lewis bases to HFIP is produced.

Experimental Section

General Considerations.

All used compounds were stored and used into a dry and argon filled glove box. Chlorobenzene was purchased from Sigma Aldrich, distilled over calcium hydride and degassed prior to use. HFIP (**1**) was purchased from Sigma Aldrich and used as received. Sulfoxides **2a-c** were prepared according to literature procedures.^[18] and used as received after checking their purity by ¹H NMR spectroscopy. Aniline (**2d**) and pyridine (**2e**) were purchased from Sigma Aldrich, purified over silica and degassed prior to use. quinoline (**2f**) and benzo[*h*]quinoline (**2g**) were purchased from Sigma Aldrich, purified over silica, recrystallized from pentane and used after checking its purity by NMR. Dioxane (**2h**) was purchased from Sigma Aldrich, distilled over calcium hydride and degassed prior to use. All 1D NMR measurements (¹H (300 and 500 MHz) and ¹³C (126 MHz)) were performed on Bruker DPX 300, Avance I 500 and Avance III 600 spectrometers. Used deuterated solvent was chloroform-*d*₁. NMR spectra were recorded at 25°C and referenced to the residual proton and carbon signals of the deuterated solvent (¹H, ¹³C). ¹H and ¹³C signals are reported relative to SiMe₄ (TMS). Chemical shifts δ and coupling constants are expressed in parts per million (ppm) and hertz (Hz), respectively. Multiplicity: s = singlet, d = doublet, t = triplet, q = quadruplet, sept = septuplet, dt = triplet of doublets, td = doublet of triplets, m = multiplet.

ITC experimental details.

Isothermal titration calorimetry (ITC) experiments were carried out on a Waters-SAS nano-ITC device (TA Instruments®)^[19] equipped with two stainless steel Hastelloy cells of 1 mL volume each. The solutions of the

adducts (**3a-h**) were prepared by dissolving same number of mol of each substrate in pure, freshly distilled and degassed chlorobenzene in the same volumetric flask. The concentrations of the solutions in pure PhCl spanned 80-130 mmol/L. Chlorobenzene was used as the solvent since it showed the best performance in regard to technical issues of our ITC experiments. ITC experiments were performed using sequential injection at 25°C with a moderate stirring rate (150-200 rpm). Auto equilibration of the ITC was performed before every experiment to reach an acceptable baseline. In a typical ITC experiment, the solution of the adduct was introduced in the servo-controlled ITC syringe (100 μ L) while the reference and sample cell were entirely filled with pure PhCl (1.0 mL). The content of the syringe was injected into the sample cell in 45 equivalent injections (2.06 μ L per injection) with a time delay between two consecutive injections spanning 1500-3000s that was adjusted to each particular system. For each studied system at least three experiments under the same condition were carried out for reproducibility. The heat of dilution of each substrate in neat PhCl was estimated from blank experiments with a solution of HFIP injected into neat PhCl (performed under the same condition as the main experiments), since HFIP has a significantly larger heat of dilution compared to the heat of dilutions of other substrates. Therefore, a heat value of 100 μ J was subtracted from all the corresponding titration curves. Enthalpy of dissociation (ΔH_d) (as result of experiment) was obtained by fitting the whole thermogram by the dimer dissociation model of Cooper *et al.*^[15] Resulting ΔH_d values represents an average value of three identical experiments.

Static DFT-D calculation details.

All computations were performed by the methods of the density functional theory (DFT) using Gaussian 09 program package.^[20] All the geometry optimizations and computing of interaction energies were employed Perdew-Burke-Ernzerhof (PBE)^[21] functional augmented with Grimme's D3^[22] inclusion of mid-to-long range dispersion force with a Becke-Johnson (BJ).^[22b] All computations were carried out with Karlsruhe's valence polarized triple- ζ (def2-TZVP).^[23] Geometry optimizations by energy gradient minimization were carried out with an ultra-fine integration grid, an energy gradient convergence criterion of 1e^{-3} au and tight SCF convergence criterion (1e^{-7} au). Implicit solvation by chlorobenzene was accounted for by employing standard solvation method - Polarizable Continuum Model (PCM)^[24] with default solvent parameters. All the geometry optimizations were confirmed as true energy minima by calculating vibrational modes. Calculations of vibrational modes (analytical second derivative of vibrational frequencies)^[25] were performed at 298.15 K at the same level of theory as the geometry optimizations calculations (i.e. at PBE-D3(BJ)/def2-TZVP level). The vibrational modes were also used to obtain thermodynamic parameters of the systems (internal energy and entropy) by statistical thermal analysis. Enthalpies and Gibbs free energies of the systems are deduced from the internal energies and entropies. Enthalpies (ΔH_d), Gibbs free energies (ΔG_d), entropies (ΔS_d) as well as energies of interactions (ΔE_a) of the pair formation are calculated as a difference between corresponding values of the pair and free reactants. All computations were performed at 298.15 K and 1 atm. Graphical representations of molecular structures were drawn using Mercury v4.1.0.^[26] Starting geometries of the monomers (**1** and **2a-h**, see Scheme 1) were taken either from the Cambridge Structural Database (CSD)^[27] or built up from similar ones and optimized as singlet ground states. In accordance to the fact that a starting geometry has great directing course to geometry optimization (as frequently it stops into some of local energetic minimum), geometries of the complexes (dimers) were constructed from the previously optimized monomers following two main possible orientations: - in case of the sulfoxides (**2a-c**) a) when the OH group of HFIP is close to the sulfur atom or b) when the OH of HFIP group is close to the oxygen atom; - in case of amines/dioxane (**2d-h**) a) when the OH group of HFIP is close to the nitrogen/oxygen atom while the rest of the HFIP molecule is above the aromatic/aliphatic ring of the amine/dioxane or b) when the OH group of HFIP is close to the nitrogen/oxygen atom while the rest of the HFIP molecule is outside of

the aromatic/aliphatic ring of the amine/dioxane, and optimized as singlet ground states. The complexes of chlorobenzene (**4**) and all the Lewis bases (**2a-h**) and HFIP (**1**) were considered as well. Geometries of these dimers (**4/2a-h**, **4/1**) were constructed from the previously optimized monomers with respect to a position of the chlorine atom (from PhCl) towards the hetero atom (from the Lewis base) and optimized as singlet ground states. Initially, all the calculations were performed in gas phase, while only most stable geometries of dimers were recalculated in chlorobenzene PCM solution phase. NCI plots^[28a] (**3b**, Figure 3) were drawn with ADFview^[28b] from singlet state gas phase geometries optimized at the ZORA-PBE-D3(BJ)/all electron TZP level using the SCM-ADF^[28b] software.

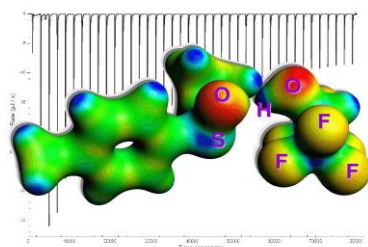
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Keywords: Hexafluoroisopropanol • Lewis adducts • Isothermal Titration Calorimetry • Density Functional Theory • Solution • Solvation

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Entry for the Table of Contents

The formation of Lewis acid-base complexes between HFIP (Lewis acid) and a series of different Lewis bases (sulfoxides, amines, dioxane) was examined by Isothermal Titration Calorimetry (ITC) experiments and static Density Functional Theory augmented with Dispersion (DFT-D) calculations.