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Robert Pollice, Marek Bot, Ilia J. Kobylianskii, Ilya Shenderovich, Peter Chen*

Abstract

London dispersion constitutes one of the fundamental interaction forces between atoms and between molecules. While modern computational methods have been developed to describe the strength of dispersive interactions in the gas phase properly, the importance of inter- and intramolecular dispersion in solution remains yet to be fully understood because experimental data are still sparse in that regard. We herein report the detailed experimental and computational study of the contribution of London dispersion to the bond-dissociation of proton-bound dimers, both in the gas-phase and in dichloromethane solution, showing that attenuation of inter- and intramolecular dispersive interaction by solvent is large (about 70% in dichloromethane), but not complete, and that current state-of-the-art implicit solvent models employed in quantum-mechanical computational studies treat London dispersion poorly, at least for this model system.

Introduction

London dispersion forces are one among several non-covalent intra- and intermolecular interactions which determine molecular geometries and energies. They depend principally on polarizability¹, and in modern treatments, can be represented by the sum of atom-pairwise interactions,² or by the interaction of exposed surfaces.^{3–5} Accordingly, one may expect that the absolute magnitude of London dispersion forces becomes significant, meaning that it reaches a range of many kcal/mol or more, for interactions between "large" molecules or fragments of molecules. Recently, this viewpoint has been expressed as an explanation for the unexpected stability of bis(diamondoid) hydrocarbons with C–C bond lengths up to 1.704 Å showing remarkable thermal stability up to 200 °C.⁶ From that, one may infer that "large" encompasses organic molecules of distinctly modest size, at least with respect to reagents, ligands or catalysts in organic and organometallic chemistry.

The size-scaling, and the universality, of London dispersion interactions, make them accordingly interesting as a potential handle for the design of molecular structures and properties, especially with the introduction of so-called dispersion energy donors (DEDs)⁷ as design elements for chemical selectivity. It had been argued first by Houk⁸, and later others^{6,9}, however, that the significant attractive dispersive interactions expected from computational results, as well as qualitative theory, appear primarily in gas-phase dissociation energies, these attractive dispersive solute-solute interactions between two incipient solute units in a dissociating molecule being largely canceled out in solution by nascent compensatory solute-solvent dispersive interactions when the dissociation occurs in solution. A complete compensation, if it were established to be general, would obviate the possibility of extending dispersion-based design concepts worked out for isolated molecules to applications in solution.

We report an experimental and computational study of the dissociation of a series of systematically varied, well-characterized, well-behaved model compounds in which we (*i*) quantify the impact of attractive dispersive interactions on the gas-phase dissociation energies, ΔE_{diss} , both by computation and experiment; (*ii*) measure $\Delta_R G_{diss}$ in solution over a wide temperature range for the same systems that we examined in the gas phase and (*iii*) test quantitatively the adequacy of the current generation of dispersion-corrected implicit solvent models for the translation of gas-phase (reaction)

thermochemistry into solution. Although the chosen model systems are particular, their behavior is general, making the present experimental and computational study relevant for essentially all processes where a chemical bond is made or broken in solution for molecules larger than a handful of atoms. Additionally, the extensive thermochemical measurements represent a consistently treated block of quantitative data for the assessment of the adequacy of computational solvent models for thermodynamics and reactions in condensed phase.

Roadmap of the Report

In order to guide the reader through this manuscript we have summarized the main scientific questions and tasks in a roadmap in Scheme 1.

Scheme 1. Roadmap of scientific questions and tasks to be tackled throughout this report.



We have divided the scientific questions into three equally important parts, computational investigation, the experimental investigation and the comparison of theory and experiment. For every section we have formulated the most important scientific questions, highlighted in green, and listed the main tasks, highlighted in red, needed to answer these questions (cf. Scheme 1). This structure will be kept for the entire report.

Experimental Section and Computational Details

 Threshold-collision-induced-dissociation (T-CID) experiments were performed on a customized Finnigan MAT TSQ-700 ESI-MS/MS spectrometer. Variable-temperature NMR experiments were performed on a Bruker AVIII-500 equipped with a BFFO broadband probe. NMR spectra were recorded every 5 - 10 °C from about -100 °C to 30 °C, in general. NMR samples were prepared inside a glove-box under N₂ atmosphere and transferred into Young NMR tubes for subsequent analysis. Highly activated molecular sieves were prepared by drying at 700 – 800 °C and 10^{-2} mbar overnight. Dry CD₂Cl₂ was prepared by stepwise static drying over 20% (m/V) highly activated molecular sieves for several days (residual H₂O at least ≤ 0.1 ppm on the basis of ¹H-NMR analysis) and degassed by 2 successive freeze-pump-thaw cycles prior to use. Isothermal titration calorimetry (ITC) was performed on a MicroCal VP-ITC.

The theoretical approach we adopted in this work is illustrated in Scheme 2. It defines a few physical quantities that are central for the investigation of gas-phase bond dissociations.

Scheme 2. Theoretical approach to compute bond dissociation energies (BDE), bond interaction energies (BIE) and deformation energies (E_{def}) illustrated on a complex A—B.



The BDE is the energy difference between the monomers and the dimer at their respective groundstate geometries. Following the usual logic in energy decomposition schemes, the bond interaction energy (BIE) is the energy difference between the dimer and the monomers at the dimer geometries. The overall deformation energy (E_{def}) is the energy difference between monomers at the dimer geometry and the monomers at their ground-state geometries, reminiscent of the inner-sphere reorganization energies in Marcus theory. These quantities are central for this work.

Geometry optimizations were performed using Orca¹⁰ (version 3.0.3, unless noted otherwise) employing GGA (BP86^{11,12}, B97-D3¹³) or meta-GGA (M06-L¹⁴) functionals in conjunction with the truncated triple-zeta basis set pc-2-sp(d)^{15,16} using the Resolution of Identity¹⁷⁻¹⁹ (RI) approximation to speed up calculations significantly. Electronic energies from density functional theory (DFT) calculations were extrapolated to a complete basis set (CBS)²⁰ and corrected for the zero-point vibrational energy. Entropic contributions were estimated using the quasi-rigid rotor harmonic oscillator approach²¹. In addition, single-point energies at the DLPNO-CCSD(T)^{22,23}/CBS²⁴ level of theory using the NormalPNO threshold²⁵ were computed on the basis of the geometries obtained at the DFT level of theory. Solvent corrections were estimated using either SMD⁵ as implemented in Gaussian 09²⁶ (revision D.01) or COSMO-RS^{27,28} as implemented in ADF 2014²⁹ using the ADF combi2005 parameters. Energy decomposition analysis (EDA) was performed using symmetry-adapted perturbation theory^{30,31} as implemented in PSI4³² (version 1.0rc). Analysis of weak non-

covalent interactions (NCI) on the basis of the reduced density gradient and the electron density was carried out using NCIPLOT 3.0^{33,34} and visualized using PyMOL³⁵ (version 1.8.4).

More detailed information about test substance synthesis, T-CID measurements, variabletemperature NMR studies, control experiments and computational studies is provided in the Supporting Information.

Results of Computational Investigation

Are proton-bound dimers a good system to test for the contribution of London dispersion to the bond dissociation energy?

A good set of systems to test for the contribution of London dispersion to the BDE should comprise molecules with a common underlying structure. We designed test systems consisting of two main fragments that are connected by a relatively weak central bond, which is nevertheless strong enough to determine the geometry of the adduct, meaning the relative positions and orientations of the two fragments that are to separate in the dissociation. The two fragments carry substituents which are largely remote from the central bond, and which interact with each other mainly by dispersion (Scheme 3). Furthermore, these substituents should have conformational flexibility as limited as possible to minimize entropic contributions.

The idea is that, upon bond cleavage the inter-fragment dispersive interactions are lost, effectively making the (free) energy of bond dissociation a function of the substituent, and, thereby, a function of London dispersion. While this dispersive attraction is strong in the gas phase, it is at least partially compensated by additional interactions with solvent molecules in the two fragments compared to the initial complex for the comparable dissociation in solution (Scheme 3). By comparison between gas phase and solution, the degree of compensation from the dispersive interactions with the solvent can be estimated.

In addition, the set of model compounds should be well-behaved with respect to electronic structure calculations (both standard DFT and wavefunction methods), i.e. they display no pathologies in their bonding which could obscure the intermolecular interactions that we probe experimentally with T-CID measurements in the gas-phase and NMR studies or calorimetry in solution. Lastly, the test systems with systematically variable substituents need to be synthetically accessible at a reasonable effort, small enough to investigate computationally at a reasonable effort, and amenable to experimental investigations in the gas-phase, e.g. by electrospray ionization tandem mass spectrometry (ESI-MS/MS), and in solution, by equilibrium measurements (e.g. spectroscopic studies, calorimetry). We chose symmetric proton-bound dimers of organic mono-nitrogen bases (i.e. pyridines, guinolines, acridines and tertiary amines, cf. Scheme 3) as our test systems in this work for several reasons. First of all, H-bonded systems in general are well-studied both experimentally and computationally, and are known to behave well in quantum mechanical calculations, i.e. their bonding should be properly described in standard electronic structure calculations, and many benchmarks have been published for them facilitating the choice of good computational methods.^{36–} 38 To minimize the chances that multireference character would complicate the calculation, we looked at the T1 diagnostic³⁹ obtained from DLPNO-CCSD(T) calculations. Not a single value above 0.014 was observed; most values were close to 0.010 (i.e. far from the threshold of 0.020), strongly suggesting the absence of any significant multireference character for all test systems investigated.

Scheme 3. Design of test systems for bond dissociation reactions to study London dispersion in the gas phase and in solution.



Moreover, these systems can be readily followed by standard spectroscopic techniques like ¹H-NMR in solution⁴⁰ and, since they are charged, are, in principle, also amenable to T-CID experiments in the gas-phase. Lastly, good synthetic building blocks are readily available and many reliable synthetic protocols are published in literature, which allows us to build rapidly a library of these compounds. The structures of all the model compounds investigated in this work are shown in Scheme 4.

Scheme 4. Structures of the model compounds investigated in this work with corresponding color coding used in diagrams throughout the manuscript to illustrate data. Compound **29** is displayed in violet (vide infra), but belongs to the group of pyridines with large substituents.



The last, and probably most important, task in this section is to test whether the contribution of London dispersion to the BDEs of our proton-bound dimers indeed is large and to estimate its relative importance compared to other energy components. To make that determination, we applied symmetry-adapted perturbation theory^{30,31} (SAPT) to obtain the contributions of electrostatics, exchange, induction and dispersion to the corresponding BIEs (Figure 1).



Figure 1. Energy components of BIE obtained from SAPT (sSAPTO/jaDZ level of theory using B97-D3/pc-2-sp(d) geometries, vide infra) of all proton-bound dimers (left-hand diagram) and exchange and dispersion energy components, relative to the proton-bound dimer of unsubstituted pyridine (in the ordinate values) together with their sum (right-hand diagram). All the numerical results are listed in the Supporting Information. The upper "limit" in BIE of about -30 kcal/mol corresponds to the BIE of unsubstituted pyridine and other "small" pyridines.

On the basis of Figure 1 several important observations are made. First of all, the contribution of London dispersion shows the largest slope with respect to the change in BIE as the substituents are varied, showing that the main change in BIE stems from a change in dispersion in the systems investigated. Secondly, exchange shows a counteracting trend compared to dispersion (and electrostatics). Thirdly, in the gas-phase, attractive dispersion wins over repulsive exchange in our systems (Figure 1, right-hand diagram), as indicated by the positive slope in the sum ($E_{ex}+E_{disp}$), albeit with the proviso that the latter small positive slope is the small difference between two, much larger, numbers. Altogether, our proton-bound dimers are therefore good systems to test for the contribution of London dispersion to the BDE.

What is the magnitude and trend in computed gas-phase bond dissociation energies $\Delta_R E_{diss}$ of proton-bound dimers?

To answer the question, our computational approach was to perform geometry optimization and zero-point energy (ZPE) corrections with a computationally efficient, but still sufficiently accurate, DFT method, and then to test a few more methods to compute electronic energies, including the computationally more expensive and more robust DLPNO-CCSD(T)^{22,23} method. In this work we decided to employ the truncated triple-zeta basis set pc-2-sp(d)^{15,16} as a compromise between computational efficiency and chemical accuracy. The pc-n basis sets are optimized for DFT calculations¹⁵ and can be systematically extrapolated to the CBS limit.²⁰ Evaluation of a few functionals shows that dispersion-corrected non-hybrid functionals (B97-D3, M06-L) give very comparable results in terms of geometry, as opposed to a non-dispersion corrected one (BP86), as can be expected (Details in the Supporting Information). As an initial reality check of our DFT geometries we compared the computed gas-phase geometry of the proton-bound dimer of **19** (cf. Table 1) to the corresponding X-ray structure we obtained (cf. Figure 2).

Table 1. Comparison of experimental X-ray structure of the proton-bound dimer of 2,6dibenzylpyridine (**19**, cf. Scheme 4) and the corresponding computed structures.

Property	Experiment	BP86/pc-2-sp(d)	M06-L/pc-2-sp(d)	B97-D3/pc-2-sp(d)
N – N distance [Å]	2.80	2.83	2.79	2.78
RMSD ^a [Å]	0.00	0.38	0.17	0.14

^aRoot mean square deviation of atomic position (excluding H atoms) compared to the X-ray structure.



Figure 2. ORTEP diagrams of proton-bound dimer of **19** with 50% probability thermal ellipsoids. H atoms: white, C atoms: grey, N atoms: blue. The $[BArF_{24}]^-$ counterion is omitted for clarity. Left: View upon the whole molecule. Right: View along the N-H-N bonds showing the symmetry of the dimer. N—H (short) = 1.02 Å. N—H long) = 1.78 Å. H— π (C=C, short) = 2.54 Å. H— π (C=C, long) = 2.58 Å.

Figure 2 illustrates that the proton-bound dimer of **19** has a highly symmetric (point group C_2 , close to point group S_4) and very compact structure. The phenyl rings are arranged on the outside of the central N-H-N hydrogen bond, effectively shielding the inside within a mantle of aromatic rings. In addition, there are close C-H— π contacts between one of the two benzylic hydrogens in each methylene group and one of the C=C double bonds in the aromatic ring (CH distances 2.60 Å and 2.67 Å, and, 2.66 Å and 2.68 Å, respectively, are smaller than the sum of the van der Waals radii of C and H, which is 2.90 Å).⁴¹

Although the differences between M06-L and B97-D3 geometries are not very large, we decided to use the B97-D3 method for geometry optimizations for the further studies because of its significantly lower computational cost (B97-D3 is a GGA-functional, M06-L is a meta-GGA-functional) and the large number of molecules to compute. Next, we compared the BDEs of proton-bound dimers, obtained with the B97-D3/CBS, DLPNO-CCSD(T)/CBS and M06-L/CBS methods on the basis of B97-D3 geometries, against each other to find a robust computational method for energies as well. All the methods showed comparable trends in the BDEs across the complete set of model compounds; B97-D3 and DLPNO-CCSD(T) energies showed good mutual agreement, in general. However, M06-L resulted in systematically lower BDEs (vide infra). It should be noted here that comparison of M06-L BDEs, computed using either B97-D3 or M06-L geometries, resulted in differences of less than 1 kcal/mol for all tested model compounds except for one (compound **28**, for which a difference of 2.2 kcal/mol was observed), showing that B97-D3 geometries are adequate to compute M06-L single point energies.

How do we choose among the different model chemistries to compute $\Delta_R E_{diss}$ in the gas-phase?

In order to choose between B97-D3, DLPNO-CCSD(T) and M06-L as the best method to estimate energies we decided to compare the computed BDEs to experimental values. To obtain an experimental data set for calibration of the computational approach to estimate BDEs of proton-

bound dimers, we performed T-CID measurements for a small subset of our model compounds and compiled the corresponding results together with values available in the literature.⁴² The resulting experimental data-set was compared to the computed BDEs (Figure 3).



Figure 3. Comparison of BDEs (not ZPE corrected) obtained at the DFT/CBS//B97-D3/pc-2-sp(d) and at the DLPNO-CCSD(T)/CBS// B97-D3/pc-2-sp(d) levels of theory where DFT is either M06-L (blue) or B97-D3 (green). Comparison of the computed BDEs with experimental values. GEQ: Gas-equilibrium measurements, T-CID: Threshold-collision induced dissociation measurements. Enthalpies of reaction from GEQ and BDEs from T-CID were back-corrected to non-ZPE corrected BDEs using thermodynamic corrections at the B97-D3/pc-2-sp(d) level of theory. All the numerical values are available in the Supporting Information.

Figure 3 shows that while the experimental values of small test compounds (GEQ data-set and two values from the T-CID data-set) agree reasonably well with all three computational methods, the experimental values of larger (and more strongly-bound) proton-bound dimers (three values from the T-CID data-set) show acceptable agreement only with M06-L energies; significant deviations appear with regard to either B97-D3 or DLPNO-CCSD(T) energies, which both significantly overestimate the BDE of the experimental T-CID values of the larger model compounds.

In an effort to check the plausibility of the experimental T-CID values of the larger model compounds and to test the computational methods by an independent experiment, we designed a proton-bound dimer that can undergo an alternative dissociation reaction upon CID. The idea was to introduce a bond with a BDE that lies in between the values predicted by both DLPNO-CCSD(T) and B97-D3, and the values predicted by M06-L and obtained by T-CID measurements. Therefore, we decided to introduce a remote alkylnitrite moiety into compound **25** and synthesized compound **37** (Scheme 5). In a solution of a mixture of **25** and **37** we observed the proton-bound heterodimer **38** (Scheme 5) by ESI-MS. Upon CID at various collision energies, only cleavage of the H-bond was observed (Scheme 5). While both DLPNO-CCSD(T) and B97-D3 predicted the H-bond to be significantly stronger than the O-NO bond, M06-L predicted the H-bond to be significantly weaker (Scheme 5).

Scheme 5. Control experiment to test computational methods used for BDE estimation. Compound **37** containing an alkylnitrite moiety was synthesized and used to obtain proton-bound heterodimer **38** in solution. **38** was detected by ESI-MS and subjected to CID (top). Of the four possible dissociation channels (two **O-NO bond cleavages**, which are indistinguishable by MS, and two **H-bond cleavages**), only the two distinct H-bond cleavages were observed (bottom left). M06-L/CBS correctly predicts H-bond cleavage to be preferred, both B97-D3 and DLPNO-CCSD(T) predict O-NO bond cleavage to be preferred (bottom right).



1.00-		1026.60	Reaction	B97-D3/CBS [kcal/mol]	M06-L/CBS [kcal/mol]	DLPNO- CCSD(T)/CBS [kcal/mol]
90.75- 10.75-	464.80		H-bond isomerization (38b to 38a)	0.3	0.4	0.6
elative Ab			H-bond cleavage 38a	44.3	34.2	45.3
ữ _{0.25} -	543.80		H-bond cleavage 38b	45.5	35.1	44.2
0.00 - 2	50 500 750 m/z [u/e]	1000	O-NO bond cleavage 38a	40.7	40.1	38.5
			O-NO bond cleavage 38b	41.0	40.5	39.1

Scheme 5 shows that, from the computational methods used, only M06-L/CBS correctly predicts the experimentally observed CID dissociation selectivity of **38**, which also goes in line with the good agreement between BDEs estimated by M06-L and measured by T-CID experiments (Figure 3). On the basis of these results, M06-L/CBS was used as our method of choice for estimation of BDEs of proton-bound dimers.

What is the magnitude and trend in computed Gibbs free energies of dissociation $\Delta_R G_{diss}$ and its components in CH₂Cl₂ solution?

In order to estimate the Gibbs free energy of bond dissociation from gas-phase BDEs we need to estimate the gas-phase thermodynamic corrections and the Gibbs free energies of solvation. We employed the current state-of-the-art implicit, dispersion-corrected solvent models, namely SMD⁵ and COSMO-RS²⁷, which are widely employed in ab initio calculations.⁴³ The overall theoretical approach we chose is illustrated in Scheme 6.

Scheme 6. Theoretical approach to compute Gibbs free energies of bond dissociation $\Delta_R G_{diss}$ of proton-bound dimers in CH₂Cl₂ at 298 K.

$$\Delta_R G_{diss}^{\circ}(CH_2 Cl_2) = \Delta_R E + \Delta_R ZPE + \Delta_R H_{corr}^{\circ} - 298.15 \Delta_R S^{\circ} + \Delta_R G_{sol}^{\circ}(CH_2 Cl_2)$$

 $\Delta_R E$: Difference in electronic energies from single point calculations at M06-L/CBS level of theory using B97-D3/pc-2-sp(d) geometries

 $\Delta_R ZPE$: Difference in zero-point energies from B97-D3/pc-2-sp(d) level of theory assuming strictly harmonic oscillations

 $\Delta_R H_{corr}^\circ$: Difference in enthalpy corrections from B97-D3/pc-2-sp(d) level of theory assuming ideal gas behavior on the basis of a single minimum conformer

 $\Delta_R S^\circ$: Difference in entropies from B97-D3/pc-2-sp(d) level of theory assuming ideal gas behavior and using the Q-RRHO approach for low-frequency modes based on a single conformer

 $\Delta_R G_{sol}^{\circ}(CH_2 Cl_2)$: Difference in Gibbs free energies of solvation from either SMD (M05-2X/6-31g* level of theory) or COSMO-RS (BP86/TZP level of theory)

On the basis of this approach we computed $\Delta_R G^{\circ}_{diss}$ at 298 K in $CH_2 CI_2$ for all our proton-bound dimer model compounds and analyzed the Gibbs free energy decomposition of the predicted $\Delta_R G^{\circ}_{diss}$ in $CH_2 CI_2$ for both solvent models into gas-phase $\Delta_R H^{\circ}_{diss}$, gas-phase $-T \Delta_R S^{\circ}_{diss}$ and $\Delta_R G^{\circ}_{sol}$ (Figure 4).



Figure 4. Decomposition of predicted Gibbs free energy of dissociation $\Delta_R G^{\circ}_{diss}$ in CH₂Cl₂ for both SMD (left-hand diagram) and COSMO-RS (right-hand diagram) at 298 K. All the numerical results are listed in the Supporting Information. The Gibbs free energy is denoted as "Free Energy" in the diagrams.

Figure 4 clearly shows that when either COSMO-RS or SMD are used, the trend in the predicted gasphase Gibbs free energy of dissociation is governed by the trend in predicted gas-phase enthalpy. Both predicted gas-phase entropy and predicted Gibbs free energy of solvation show a counteracting trend, but the corresponding slopes are significantly smaller. From that it can be concluded that the predicted $\Delta_R G^{\circ}_{diss}$ in CH₂Cl₂ is largely governed by the gas-phase enthalpy rather than by gas-phase entropy or Gibbs free energy of solvation.

Results of Experimental Investigation in CH₂Cl₂

How do we get a consistent set of experimental $\Delta_R G_{diss}$ data in $CH_2 Cl_2$ solution for the protonbound dimers? In conjunction with theoretical studies of the bond dissociation of proton-bound dimers we synthesized protonated salts of thirty-five of our model compounds (Scheme 4, not including 28) and determined the corresponding bond dissociation equilibrium constants in dichloromethane (CD₂Cl₂) experimentally between -100 °C and 30 °C. To perform these experiments, several preconditions need to be fulfilled. First of all, since the equilibrium position is determined from the ¹H-NMR shift of the H atom involved in the H-bond, the NMR solvent needs to be extremely dry (≤ 0.1 ppm of residual water). To achieve that extraordinary degree of dryness, we performed successive stages of static drying using highly-activated molecular sieves (dried for at least 12 h at temperatures above 700 °C at 10⁻² mbar, details in the Supporting Information). Secondly, because two of the three species involved in the bond dissociation equilibrium of our proton-bound dimers have a charge of +1, counter ions must be present in the solution experiments (unlike the gas-phase measurements). To avoid differential temperature effects of ion pairing in solution, we chose for our studies the noncoordinating [BArF₂₄] counterion, which had been shown previously to be innocent in comparable experiments.⁴⁰ To test rigorously for the presence, or absence, of ion pairing in our systems, we performed DOSY NMR measurements at 298 K which indicated absence of ion pairing in our model systems under investigation (Details in the Supporting Information).

The left-hand diagram of Figure 5 shows a representative variable-temperature series of NMR spectra of **5**. In the right-hand diagram of Figure 5, the ¹H-NMR shifts of the acidic proton are plotted against temperature together with the corresponding statistical fit to estimate the experimental enthalpy and entropy of dissociation (Details of the data evaluation are described in the Supporting Information).



Figure 5. Overlay of ¹H-NMR spectra in the temperature range -100 °C to 20 °C of a mixture of diisopropylpyridine **5** and the corresponding protonated pyridinium salt ($[BArF_{24}]^{-}$ counterion) in CD₂Cl₂ (left-hand diagram) and extracted dependence of the acidic proton shift on the temperature with the corresponding fitted regression function to estimate enthalpy and entropy of reaction (right-hand diagram).

To validate the Gibbs free energies obtained from the NMR studies by an independent method, isothermal calorimetry (ITC) at 298 K on four selected test compounds was carried out, showing that the experimental values of $\Delta_R G_{diss}$ obtained from either variable-temperature NMR or ITC are within 1 kcal/mol and therefore in good mutual agreement (Details in the Supporting Information).

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Which experimental results can be used for comparison to the computed thermodynamic parameters?

From our variable-temperature NMR results we estimated enthalpies and entropies of reaction for the dissociation of the proton-bound dimer of thirty-five nitrogenous bases (cf. Scheme 4). Plotting estimated enthalpies against estimated entropies in a compensation plot^{44} showed a moderate enthalpy-entropy compensation (EEC) with a compensation temperature⁴⁴ T_c of 234 ± 25 K. While it is possible that the observed EEC is a result of correlated errors in enthalpies and entropies, a statistical p-test suggested by Perez-Benito and Mulero-Raichs in 2016⁴⁵ showed a probability of less than 0.05 that the observed correlation is explainable solely by random experimental errors (Details in the Supporting Information). However, enthalpies and entropies obtained from ITC at 298 K for selected test compounds were different compared to values obtained from the NMR studies (Details in the Supporting Information). Therefore, to take a conservative position, we only used $\Delta_R G_{diss}$ obtained from variable-temperature NMR for further comparisons to computed results.

Comparison of Theory and Experiment

Does the attractive contribution of dispersion to gas-phase bond dissociation energies survive in solution?

In order to gain insight into the transfer of London dispersion from the gas-phase into solution we plotted $\Delta_R G_{diss}$ in CD₂Cl₂ against the corresponding computed gas-phase BDE at the M06-L/CBS//B97-D3/pc-2-sp(d) level of theory (Figure 6).



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Figure 6. Experimental $\Delta_R G_{diss}$ of proton-bound dimers in CD₂Cl₂ plotted against corresponding BDEs in the gas-phase as predicted by M06-L/CBS//B97-D3/pc-2-sp(d) level of theory at low temperature (top diagram), close to the compensation temperature (middle diagram) and at high temperature (bottom diagram). The linear regression was performed with only the red data points in each diagram. The violet data point corresponds to compound **29** and is a special case which will be discussed later (vide infra). All the numerical results are listed in the Supporting Information. The Gibbs free energy is denoted as "Free Energy" in the diagrams.

At low temperature (180 K) we observed three groups of data points. "Small" systems (blue data points in Figure 6) cluster together in a very narrow area. Pyridines with larger substituents (red data points in Figure 6) showed a reasonable linear correlation between the $\Delta_R G_{diss}$ in CD₂Cl₂ and the computed gas-phase BDE, indicating that, at low temperature, the trend in Gibbs free energy is determined by the trend in the corresponding gas-phase BDE. Since the trend in the gas-phase BDE is mainly governed by London dispersion (*vide supra*) it can be inferred that, for these species, the trend in $\Delta_R G_{diss}$ in CD₂Cl₂ is mainly affected by dispersion as well, which may be regarded as a primarily enthalpic effect. At higher temperatures (240 K) the correlation is still observed but it becomes obscured by increasingly large entropic effects as the temperature is increased towards 300 K. The third group of data points consisted of quinolines with large substituents. They do overlap with the data points of pyridines with large substituents but, especially at low temperature, show no clear trend with respect to the BDE. At higher temperature, a trend is observed but with a slightly different slope compared to the pyridines with large substituents.

Do the implicit solvent models treat the bond dissociation equilibria of proton-bound dimers in CH_2Cl_2 solution adequately?

To test whether dispersion-corrected implicit solvent models treat the bond dissociation equilibria adequately, we compared computed $\Delta_R G^{\circ}_{diss}$ at 298 K in $CH_2 Cl_2$ for all our proton-bound dimer model compounds against the corresponding experimental values at the same temperature (Figure 7).



Figure 7. Comparison of $\Delta_R G^{\circ}_{diss}$ in CH₂Cl₂ from computations ($\Delta_R G^{\circ}_{pred}$) and from experiment ($\Delta_R G^{\circ}_{exp}$) using SMD (left-hand diagram) and using COSMO-RS (right-hand diagram) for the Gibbs free energies of solvation. All the numerical results are listed in the Supporting Information. The Gibbs free energy is denoted as "Free Energy" in the diagrams.

While both SMD and COSMO-RS adequately predict the Gibbs free energy of dissociation (meaning to chemical accuracy of ± 1 kcal/mol) for some small subset of the thirty-five proton-bound dimers (Scheme 4) for which we have solution data, it is difficult to find a systematic pattern which would serve as a marker for reliability of either model. Both implicit solvent models fail spectacularly in reproducing the trends in Gibbs free energies of bond dissociation when going from small to large test systems.

Discussion

Taking the reported results at face value leads one directly to the three main conclusions of this study:

- The attractive part of the intermolecular potential due to London dispersion contributes substantially to the BDE in the gas phase as the substituents are made systematically larger, giving a chemically significant increment of up to about 10 kcal/mol for molecules in the range of 50 – 100 heavy (non-hydrogen) atoms.
- ii. Going from the gas-phase into dichloromethane solution, the BDE is attenuated by approximately 70% through compensatory interactions of solvent molecules with parts of the molecule newly exposed upon cleavage of the bond.
- iii. Implicit dispersion-corrected solvent models reproduce neither the trend nor the magnitude of $\Delta_R G_{sol}$ adequately, at least for the test systems examined in this study.

Whereas the present study was done for a carefully constructed test series of molecules, the universality of dispersive interactions should mean that the claims apply more generally to other bond-making and bond-breaking processes in the gas phase and in solution. General claims, however, demand a critical evaluation of the data, especially with regard to how they would apply to other, perhaps less clearly controlled, systems. Accordingly, the three claims are examined sequentially.

Theoretical and Experimental Investigation of Gas-Phase Bond Dissociation. To partition interaction energies into physically meaningful terms and elucidate corresponding trends, energy decomposition analysis (EDA) methods have been devised.⁴⁶ One of the most popular approach in that regard is

symmetry-adapted perturbation theory (SAPT)^{30,31} that treats the interaction between two fragments as a perturbation to the isolated fragment Hamiltonians, and breaks down the interaction into electrostatics, exchange, induction and dispersion in a physically well-defined way.³¹ Using SAPT we could show that the differences in the BIEs of our model compounds are indeed mainly governed by dispersion in the gas-phase (Figure 1). Significant attractive contribution also arises from increasingly favorable electrostatic interactions which we would *post facto* attribute mainly to quadrupolequadrupole interactions. While formally not included in the dispersion term, these favorable interactions would increase, as well, with growing dispersive attraction, and provide additional stabilization in alkyl- and aryl-substituents that had been designated dispersion energy donors (DED).

The importance in DFT of treating noncovalent interactions at medium-to-large distances properly is well established in the field.² The various approaches to account for non-bonded interactions in both hydrogen-bonded systems and dispersion-bound systems were benchmarked thoroughly by Sherrill.³⁶ In addition, computationally efficient, highly accurate and less empirical wavefunctionbased methods have been developed recently, the most notable one, especially for the study of noncovalent interactions, being the coupled-cluster method DLPNO-CCSD(T),^{22,23} which can be readily applied to molecules up to approximately 10² atoms with current computational resources, and which has been shown in benchmark studies to provide excellent accuracy^{2,25,47,48}, comparable to canonical CCSD(T), for only a fraction of the computational cost and much more favorable scaling.^{23,47} We chose our general computational approach to be computationally most efficient without losing too much accuracy and rigor. B97-D3, being only a GGA functional, is known to provide excellent geometries, and also good energetics, for organic molecules at very low computational cost.³⁶ Using a reasonably large basis set (truncated triple-zeta basis) allowed us to obtain geometries reasonably well-converged to the complete basis set (CBS) limit. M06-L, a meta-GGA functional, which we used for estimating energies on the basis of B97-D3 geometries, is not much more expensive than B97-D3 and was designed inter alia for use in main-group and organometallic thermochemistry, and noncovalent interactions. For comparison, DLPNO-CCSD(T) single point calculations, at the DFToptimized geometries, allowed us to obtain high-level-of-theory energies at a reasonable computational cost.

On the basis of the current literature, we had expected DLPNO-CCSD(T) energies to be the best predictor for gas-phase BDEs of our model compounds, which is also why we used them as abscissa in Figure 3. Contrary to our expectations, it significantly overestimated gas-phase BDEs for the larger molecules, while M06-L energies appear to show better agreement to experiment. We note that the nitrite cleavage control experiment is an intramolecular competition between homolysis of the O-N bond in a nitrite and cleavage of the N-H-N ionic hydrogen bond, for which both transition states are "loose." It requires no threshold measurement, no modeling, and no treatment of kinetic shift.⁴⁹⁻⁵¹ In such a circumstance, expectations from statistical rate theory would predict selective cleavage of the weaker bond as long as the BDEs differed by more than about 2 kcal/mol.^{52,53} It requires merely the assumption that the competing dissociations within the same molecule, i.e. the cleavage of N-H-N versus the cleavage of the RO-NO bond, behave statistically. This assumption was a main theme of research in experimental chemical physics through the 1980s and 1990s, with the conclusion, summarized in many places but explicitly in reviews by Armentrout and Baer^{52,53}, that dissociations of molecular ions with more than a handful of heavy atoms are statistical, exceptions being very rare. Moreover, "Second-Law" methods, of which the T-CID experiment is a particular case, for measurement of bond energies in ions can be justified by the absence of reverse barriers in ion dissociations, a simple consequence of the long-range charge-dipole electrostatic potential for the bimolecular microscopic reverse reaction.⁵⁴ Lastly, one must consider that the ubiquitous tables of bond strengths for (neutral and charged) molecules with up to a dozen heavy (non-hydrogen) atoms, for example the JANAF tables from the NIST^{55,56}, derive overwhelmingly from data with ion-molecule reactions or dissociation of molecular ions, for which the same statistical assumption must be made. Recently, Ruscic has linked together the experimental data in "Active Thermochemical Tables", a database project^{57,58} which makes explicit the role of individual gas-phase experiments in each bond strength, and which compute the bond strengths via multiple thermochemical cycles to ensure reliability. One cannot escape the assumption of statistical behavior in gas-phase ion-molecule reactions.

It is also clear from the experimental evidence that the statistical assumption gets better as the molecules get larger, which supports the T-CID value for the BDE in the large proton-bound dimers, as well as our interpretation of the control experiment in Scheme 5. Nevertheless, the discrepancy between DLPNO-CCSD(T) bond energies, and the T-CID experiments, for the large molecules, specifically 25, 27 and 28, is unsettling. CCSD(T) is often considered the gold standard for predicting thermochemistry. While it cannot yet be excluded that the problem lies with the NormalPNO threshold used for our DLPNO-CCSD(T) calculations^{59,60}, it appears that the discrepancy in the protonbound dimers scales up with interaction strength of the N-H-N bond. All of the methods agree to better than 2 kcal/mol for dissociation of the RO-NO bond (about 40 kcal/mol) in the same, large molecule, and the corresponding fragment, NO, is so small and "hard" that the contribution of dispersion to its bond strength is negligible. For the N-H-N bond in the same molecule, the interacting groups were designed to maximize the contribution of dispersion, which strongly suggests that the contribution of dispersion to the bond strength is the difficulty in treating the N-H-N bond. This distinction strongly suggests, very surprisingly, that DLPNO-CCSD(T), and possibly any method which is referenced to canonical CCSD(T), may show a cumulative overestimation of dispersion, which only adds up to a discernible effect for larger molecules. In that regard the excellent mutual agreement between B97-D3, sSAPTO and DLPNO-CCSD(T) (Details in the Supporting Information) is not surprising considering that extensive benchmarks of these methods were carried out, showing good agreement of all these methods to high-level computations using very similar compounds.^{2,25,36-} ^{38,61} It should also be noted that the D3 correction is constructed to reproduce CCSD(T) energies and, therefore, good agreement between B97-D3 and DLPNO-CCSD(T) is not only plausible, but, in fact, to be expected.

Given the absence of other, independent benchmarks for gas-phase bond strengths in molecules with 50 – 100 heavy atoms, we therefore chose to employ M06-L as the cost-efficient method that appeared to scale up to large molecules reliably. However, the principal conclusions concerning attenuation of dispersive attraction in solution, and the poor agreement of $\Delta_R G_{sol}$ from SMD or COSMO-RS do not change if B97-D3 or DLPNO-CCSD(T) were to be used instead (Supporting Information).

Experimental Investigation of Bond Dissociation Equilibria in Solution. In solution, intramolecular London dispersion is attenuated because of competitive intermolecular interactions with solvent molecules.⁸ In non-hydrogen-bonding solvents, solvent molecules interact with solute molecules, to a large extent, by dispersion and electrostatics, compensating intramolecular (dispersive) interactions lost upon cleavage of a bond by roughly comparable intermolecular (dispersive) interactions that effectively diminish the importance of intramolecular dispersion. Ultimately, it is then a balance between intermolecular solute-solvent interactions and both intramolecular dispersive interactions

and intermolecular solvent-solvent interactions that determine the position of the folding equilibrium⁹, as had been noted in experiments with molecular torsion balances.⁶² While it is known that attenuation of London dispersion in solution is, in general, large, to the best of our knowledge, the actual extent of attenuation for at least one single solvent has not been reported before. An early computational study employing force fields in combination with a dispersion-corrected implicit solvent model investigating the attenuation in molecular balances was reported by Houk in 1999.⁸ He could show that solute-solvent dispersion forces in an organic solvent have a significant influence on the conformational preference of several molecular balances.⁸ Furthermore, there have been several systematic experimental studies by Cockroft,^{9,63,64} investigating the importance of dispersion in folding equilibria of molecular balances showing that intramolecular dispersion does contribute significantly in solution, as do solvophobic interactions.⁶⁴ In addition, Cockroft studied the association of urea hosts with naphthyridine guests with varying substituents on both molecules experimentally and computationally to unravel the influence of aromatic stacking on the association equilibrium in solution, showing that London dispersion is not attenuated completely and indeed governs aromatic stacking in an organic solvent.⁶⁵ However, experimental data on the importance of London dispersion in solution and its attenuation are still sparse, and more systematic studies in several distinct solvents are required.

In our data we observed the presence of (moderate) enthalpy-entropy compensation (EEC)⁴⁴. This phenomenon, which is defined as a (linear) correlation between enthalpy and entropy of dissociation, has been reported in a wide range of different chemical processes and physical phenomena and has been widely discussed in literature.^{44,66–70} While there are several proposed origins of EEC, amongst the most commonly discussed are systematic correlated errors in the determination of enthalpy and entropy, on the one hand, and environmental processes like solvent reorganization as a universal mechanism for EEC^{44,69}, on the other. In either case, the ramifications for the interpretation of the data are the same. EEC makes the independent interpretation of enthalpy and entropy, at best, very difficult, and, in general, non-intuitive.⁶⁹ Regardless of the origin, however, the experimentally-determined Gibbs free energies are generally unaffected by EEC and can therefore be readily interpreted.^{44,69} We choose to interpret the data using the secure $\Delta_R G^{\circ}_{diss}$ values with minimal recourse to $\Delta_R H^{\circ}_{diss}$ and $\Delta_R S^{\circ}_{diss}$ values that may admit controversy without adding much additional insight. We intend to revisit the issue with measurements of the equilibria that do not rely solely upon the temperature-dependence of $\Delta_R G^{\circ}_{diss}$, the first of which (ITC measurements on **1**, **12**, **29** and **35** at 25 °C) being already given in Table S43.

It should be noted that $\Delta_R H^{\circ}_{diss}$ and $\Delta_R S^{\circ}_{diss}$ obtained from variable-temperature NMR measurements and from ITC measurements did not show good agreement. Disagreement between enthalpies of reaction (and therefore entropies of reaction) obtained from van't Hoff plots and calorimetric measurements has been observed before several times.^{71–73} These discrepancies originate from methodological differences in the determination of $\Delta_R H^{\circ}_{diss}$. In the ITC experiments the heat of reaction is directly measured at a constant temperature. In the NMR experiments, both $\Delta_R H^{\circ}_{diss}$ and $\Delta_R S^{\circ}_{diss}$ are estimated from the observed temperature-dependence of $\Delta_R G^{\circ}_{diss}$ using the van't Hoff equation, assuming that they are temperature-independent. This assumption is most likely not valid over a temperature range spanning more than 100 °C (experiments were conducted between -100 °C and 30 °C).⁷⁴

Accordingly, we compare experimental $\Delta_R G^{\circ}_{diss}$ to computed properties like BDE, enthalpy or entropy in the gas phase, or free energy of solvation. While there is no significant correlation with respect to

gas-phase entropy, there is some correlation with both gas-phase enthalpy and free energy of solvation (Details in the Supporting Information). The most pronounced trends, and also a clear classification of the data points is, however, only observed when looking at $\Delta_R G^{\circ}_{diss}$ as a function of the corresponding gas-phase BDEs (Figure 6). It should be noted here that a comparable classification of data points is observed when B97-D3 energies are used (Details in the Supporting Information).

From Figure 6 it can be clearly seen that there are three classes of data points. The blue data points correspond to pyridines with rather small substituents in the 2 and 6 positions. The gas-phase BDEs for these compounds are all rather similar because attractive dispersion and Pauli repulsion more or less cancel each other out, making these compounds not suitable to estimate attenuation of dispersion in solution. Substituents in the 2 and 6 position of pyridine increase attractive dispersion in the corresponding proton-bound dimers, but also increase Pauli repulsion, which leads to larger equilibrium N–N distances (and distorted N-H-N angles, cf. Supporting Information).

The red data points in Figure 6 correspond to pyridines with bigger substituents showing large differences in their gas-phase BDEs because, while some compounds show a rather large intramolecular repulsion resulting in distorted N-H-N hydrogen-bond geometries, many of them also show very large, attractive dispersion compensating for the loss in bond energy from the hydrogenbonds. At low temperature, the corresponding $\Delta_{R}G^{\circ}_{diss}$ values show a significant correlation with the gas-phase BDEs, suggesting that the trend in Gibbs free energy in solution originates from corresponding trends in the gas-phase energies. By looking at the slope of the linear correlation between $\Delta_{\mathsf{R}}\mathsf{G}^{\circ}_{\mathsf{diss}}$ and BDE one can estimate the extent of attenuation of the change in gas-phase bond energy in CD₂Cl₂ solution at different temperatures (the slope corresponds to the ratio of $\Delta \Delta_R G^{\circ}_{diss}$ and ΔBDE). Therefore, we would estimate overall bond energy compensation in dichloromethane for these model compounds to be 65% - 78% at 180 K - 300 K. This number suggests that, even though attenuation is large, it is still far from complete, at least in CD₂Cl₂. While this number corresponds to a general attenuation of interactions in solution in the corresponding proton-bound dimers - our chosen test system - it is likely to reflect the compensation of London dispersion because the trend in gas-phase BDEs in these compounds is governed mostly by dispersion (Figure 1).

It should be noted that, in general, the energetic origin of the attenuation observed is both enthalpic and entropic in nature, and that there is also a significant gas-phase entropic contribution. While we expect attenuation due to Gibbs free energy of solvation to be most important, the contribution of gas-phase entropy should not be neglected a priori. Looking at our computed gas-phase Gibbs free energies of dissociation at 298 K and correlating them to the corresponding gas-phase BDEs we obtain an attenuation due to gas-phase entropy by about 20% (Details in the Supporting Information), which, while significant, is not the major fraction of overall attenuation; the solvent contribution is more important, the more so at lower temperatures. However, the significant contribution of entropy suggests that, should one try to maximize attractive effects of London dispersion at higher temperatures, it is also important to minimize entropic factors, hence flexibility of the so-called dispersion-energy-donor (DED) should be minimized. This is well demonstrated by the purple data point in Figure 6 of the proton-bound dimer of 29. While at 180 K the data point perfectly fits to the other red data points, at higher temperatures, $\Delta_{\rm B} G^{\circ}_{\rm diss}$ is much larger than would be expected from the trend of the other data points. The proton-bound dimer of compound 29 has a very rigid geometry in which basically only the tBu-groups connected to the alkyne are able to rotate but their location in space is fixed.

The green data points in Figure 6 correspond to quinolines with larger substituents showing very much larger gas-phase BDEs than the other compounds. However, compared to the pyridines with large substituents discussed before, especially at lower temperatures, a much larger attenuation of gas-phase bond energies is observed. That might be explained by the distinct structure of the proton-bound dimers of the substituted quinolines compared to the corresponding pyridines as illustrated in Figure 8.



Figure 8. Intermolecular 3D-NCI plots of the proton-bound dimers of **19** (two left-hand images), and **30** (two right-hand images) on the basis of optimized structures at the B97-D3/pc-2-sp(d) level of theory. Attractive interactions are shown in blue, repulsive interactions are depicted red (Details in the Supporting Information).

Error! Reference source not found. shows intermolecular 3D-NCI plots of the proton-bound dimers of **19** and **30**. In both cases, the phenyl rings arrange around the central N-H-N bonds to maximize intermolecular dispersion. The main difference between the 2,7-disubstituted quinolines as compared to the corresponding 2,6-disubstituted pyridines is the additional free space around the central N-H-N bonds, which, according to the colors in Figure 8, minimizes repulsion. The proton-bound dimers of the quinolines may therefore be regarded as less compact. The free space is sufficiently large to make it possible for one or more solvent molecules to be "inside" the dimers, effectively increasing attenuation of overall interaction compared to the pyridines. As a consequence, the green data points are excluded from estimating the attenuation of dispersion in dichloromethane. One experimental observation supporting this hypothesis is the observed better solubility of the 2,7-disubstituted quinoline dimers compared to the corresponding pyridines. Further investigation is required in that regard, but it already shows that close contacts of DEDs are required to maximize dispersive contributions in solution.

An alternative and simpler approach to estimate roughly the overall bond energy compensation in dichloromethane for our model compounds is based on calculating the ratio of the ranges of calculated gas-phase BDEs and experimental $\Delta_R G^{\circ}_{diss}$ values in solution. Looking at all our compounds,

the range in gas-phase BDEs is 26 kcal/mol, the range in $\Delta_R G^{\circ}_{diss}$ in dichloromethane is 5.5 – 6.3 kcal/mol at 180 K – 300 K. The corresponding ratio would be 21 – 24% which indicates an overall bond energy compensation in dichloromethane for our model compounds of 76 – 79% at 180 K – 300 K, which is comparable to the estimate obtained before (*vide supra*).

Comparison of Computed and Experimental Free Energies in Solution. The theoretical prediction of thermodynamic and kinetic parameters for chemical reactions in solution remains still one of the big challenges in computational chemistry.^{75–77} The two main theoretical approaches in that regard are direct computations in solution with or without molecular dynamics, on the one hand, and employing thermodynamic cycles starting from gas-phase parameters and adding Gibbs free energies of solvation on top, on the other. Both approaches are, in principle, compatible with either implicit^{43,78,79}, explicit,^{80,81} or hybrid⁸² solvent models.⁷⁷ While direct computations in solution using explicit solvent models would probably be most attractive from a theoretical point of view, it still is a great challenge in the field and requires very large computational resources and special expertise, explaining the still limited number of publications adopting it.^{80,81} In conjunction with guantum mechanical calculations of small-to-medium-sized molecules, and their reaction pathways, implicit solvent models are by far the most often used in the present literature. They are readily affordable computationally. They are implemented in basically all of the electronic structure calculation packages available. They can be executed in an equivalent way as standard DFT and wave function computational methods. Lastly, they appeared to be reasonably accurate.^{5,83–86} Hybrid approaches, in which a few solvent molecules are treated explicitly in the quantum mechanical calculations, and then combined with implicit models, have also been reported.^{87,88} For this study, we chose to use two of the more popular implicit solvent models, namely SMD⁵ and COSMO-RS^{27,28} (two methods explicitly accounting for dispersive interactions with solvent), using the thermodynamic cycle approach to obtain Gibbs free energies of solvation (which also is the approach used for parametrization of these solvent models^{5,27}) and adding them to the results of our quantum mechanical calculations (Scheme 6). Comparing the predicted Gibbs free energies of dissociation in CH₂Cl₂ to our experimental values is then also a direct test of the adequacy of these solvent models in systems having large contributions of London dispersion towards the overall binding energy. It should be noted here that our experimental values are obtained in CD₂Cl₂, and therefore one could expect a solvent equilibrium isotope effect (EIE). However, this EIE, originating from non-covalent interactions, is expected to be close to 1 and therefore negligible.⁸⁹

The comparison of predicted and experimental Gibbs free energies in Figure 7 clearly shows that, while for both SMD and COSMO-RS the overall thermodynamics of the bond dissociation in CH_2Cl_2 of some subset of the model compounds may be reasonably well predicted, the deviations when going to systems with either smaller or larger gas-phase BDEs become larger (the largest deviations of prediction from experiment reach about 12 kcal/mol, which corresponds to more than 8 orders of magnitude in the equilibrium constant at 298 K). The deviations become not only very sizable, they are also systematic. Depending on which computational approach was used (SMD or COSMO-RS for Gibbs free energies of solvation), the intersection between predicted $\Delta_R G^{\circ}_{diss}$ values and a correlation line through all the experimentally determined values changed, but in both cases the change in $\Delta_R G^{\circ}_{diss}$ when going from model compounds with small, to ones with large, contribution of dispersion was predicted incorrectly. *A priori*, there could be three main sources of the large deviation observed. First, the electronic energy difference could be, in principle, the reason for the large deviation (1st term in Scheme 6). However, on the basis of our comparisons to available experimental

equilibrium measurements,⁴² to our gas-phase T-CID measurements and the CID control experiment performed (Figure 3 and Scheme 5) we expect this term to be most robust for all the model compounds investigated. Second, the gas-phase entropy difference could give rise to the large systematic deviations (4th term in Scheme 6). While it is plausible that there is a non-negligible systematic deviation in the entropies of bigger systems, as we only considered the single lowestenergy conformer for all systems, this deviation being larger, the larger and also the more flexible the substituents on the pyridines and quinolines become, it is not expected that the deviation would correlate necessarily with the gas-phase enthalpy (Figure 4).

In this regard it is interesting to look closer at the data point with the lowest predicted Gibbs free energy of dissociation in both diagrams in Figure 7. This data point corresponds to 2,6dineopentylpyridine (**14**, cf. Scheme 4). Steric constraints due to the neopentyl groups cause the proton-bound dimer to adopt a rather distorted H-bond geometry; the overall gas-phase BDE is very low because London dispersion cannot make up for the lost H-bond energy. The computational approach, regardless of solvent model used, greatly underestimates the corresponding $\Delta_R G^{\circ}_{diss}$ of **14** in CH₂Cl₂. However, because of the quite flexible, and already quite large, substituents, we would expect our computational approach to underestimate the gas-phase entropy of dissociation $\Delta_R S^{\circ}_{diss}$ rather than overestimate it, which should lead to an overestimation of the Gibbs free energy of dissociation rather than the significant underestimation observed. Overall, the type of systematic deviation of $\Delta_R G^{\circ}_{diss}$ in CH₂Cl₂ observed is not in agreement with systematic errors in gas-phase $\Delta_R S^{\circ}_{diss}$ as the principal cause and it should therefore not be the most important source of error.

Therefore, the main reason for the systematic deviation most likely originates in the contribution of the difference in Gibbs free energy of solvation (5th term in Scheme 6). First of all, the systematic deviation of computed $\Delta_R G^{\circ}_{diss}$ in CH₂Cl₂ observed, compared to experiment, could readily be explained by systematically underestimated solute-solvent attractive dispersive interactions. Considering again the proton-bound dimer **14**, the favorable dispersive interactions would probably greatly change the preferred minimum geometry when going from the gas-phase into solution. Attractive solute-solvent interactions of the neopentyl groups would effectively favor conformations with shorter N-H-N distances and an N-H-N angle closer to 180° making $\Delta_R G^{\circ}_{diss}$ in CH₂Cl₂ more favorable. Both gas-phase and solution geometries (optimized in implicit solvent) were used to estimate Gibbs free energies of solvation (Supporting Information). The corresponding results did not show big differences suggesting that the solution geometries optimized in an implicit solvent are still likely not realistic enough to obtain accurate Gibbs free energies of solvation, which is presumably a consequence of systematic underestimation of solute-solvent attraction in the solvent models used.

On the other hand, significant underestimation of solute-solvent dispersive interactions would also explain the systematic deviation observed for all the other systems. From a fundamental point of view, the large systematic deviation observed can be rationalized by considering that the implicit solvent models used (SMD and COSMO-RS, *vide supra*) account for solute-solvent dispersive attraction by a surface-dependent term.^{5,4} However, dispersion corrections employed in DFT are atom-pairwise terms, at least for the D3 correction,⁹⁰ which are, effectively, volume-based treatments of London dispersion. As one might expect, while for small systems a surface-dependent dispersion correction can give a reasonable approximation for the overall contribution and show acceptable agreement with a volume-based approach, as system size grows, systematic deviations between the two approaches are inevitable. This methodological discrepancy had been confirmed in

a benchmarking theoretical study by van Gunsteren on the basis of MD simulations of ubiquitin, showing deviations between the two approaches of up to 45 kcal/mol in solvation free energies.⁹¹ Furthermore, implicit solvent models inherently cannot account for entropy of solvation directly, giving rise to a non-negligible systematic uncertainty in the estimated Gibbs free energies of solvation.

Overall, the theoretical estimation of Gibbs free energies of dissociation in solution rely on accurate gas-phase Gibbs free energies and accurate Gibbs free energies of solvation. The former are the result of gas-phase calculations which, in the best case, can be well benchmarked for many systems, and can be quite robust, again, in the best cases, especially when state-of-the-art theoretical methods are applied and when they are calibrated against accurate gas-phase measurements. Of course, care should be taken to select methods on the basis of good benchmarks, either consisting of theoretical or experimental values, and also to consider multiple conformers (or include MD), if feasible, to treat for both enthalpy and entropy in the gas-phase properly. The limitations for larger systems are evident, and it remains to be determined what would constitute a minimal, physically realistic (meaning correct trends and orders-of-magnitude) method. At the present, the implicit solvent model calculations employed to obtain Gibbs free energies of solvation, which yield reasonable results for many systems, are used as a compromise between computational effort and theoretical adequacy, but we believe them to be the weakest link in the estimation of Gibbs free energies of dissociation in solution.

Conclusions

In this work we report an extensive study of bond dissociation equilibria of a wide variety of protonbound dimers in the gas-phase and in solution by T-CID measurements, computational methods and NMR studies. We conclude that London dispersion becomes very significant for medium-to-large molecules in the gas-phase, which was observed directly by experiment, and is always accompanied by significant contribution of repulsive Pauli exchange, which, however, does not fully compensate the attractive contribution of dispersion. The significant attractive contribution of dispersion, despite being attenuated by about 70%, still transfers into dichloromethane solution temperatures that are relevant for chemical reactions, at least for the chosen test systems, showing that altering London dispersion can indeed be a useful design principle to tune molecular stability for chemical processes in solution. Furthermore, currently employed implicit solvent models are shown to describe attenuation of dispersion in solution inadequately, especially when the corresponding contribution becomes large, showing that alternative theoretical approaches and models are required in that regard for a proper estimation of energies.

While we have chosen a specific test system for this study, our results and conclusions are not specific to that type of system. The contribution of dispersion to the gas-phase bond dissociation energies in molecular complexes decorated with increasingly large interacting hydrocarbon substituents is expected to become large for any molecular complex. Additionally, the observation that intermolecular London dispersion, while largely attenuated, still transfers into a polar organic solvent like CH₂Cl₂ is likely more general, as well, and we expect a very similar trend for other comparable organic solvents. Furthermore, the spectacular failure of implicit solvent models to predict the Gibbs free energy of dissociation in solution, suggests that these models are inadequate to describe dispersive solute-solvent interactions. Again, this is expected to be applicable not only to our test system, but in general to molecular complexes having sufficiently large interacting

 hydrocarbon substituents. Considering these points, and the wide variety of systems for which a DFT+PCM or a DFT+COSMO computational approach has been applied to in literature, we claim that our conclusions are widely applicable to homogeneous catalysis and supramolecular chemistry in polar organic solvents. Further work continuing gas-phase measurements using T-CID, investigating proton-bound dimer equilibria in different solvents and exploring alternative theoretical approaches to estimate Gibbs free energies of solvation are underway in our group.

Associated Content

Supporting Information

General experimental and computational details, MS measurement details, T-CID measurement details, NMR measurement details, syntheses of test substances, supplementary results and discussion, detailed evaluations and mathematical derivations, raw measurement data, raw computational data, source code of the modified program to perform the statistical p-test for EEC in chemical equilibria and xyz and crs files of all the model compounds.

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