Angewandte Reviews

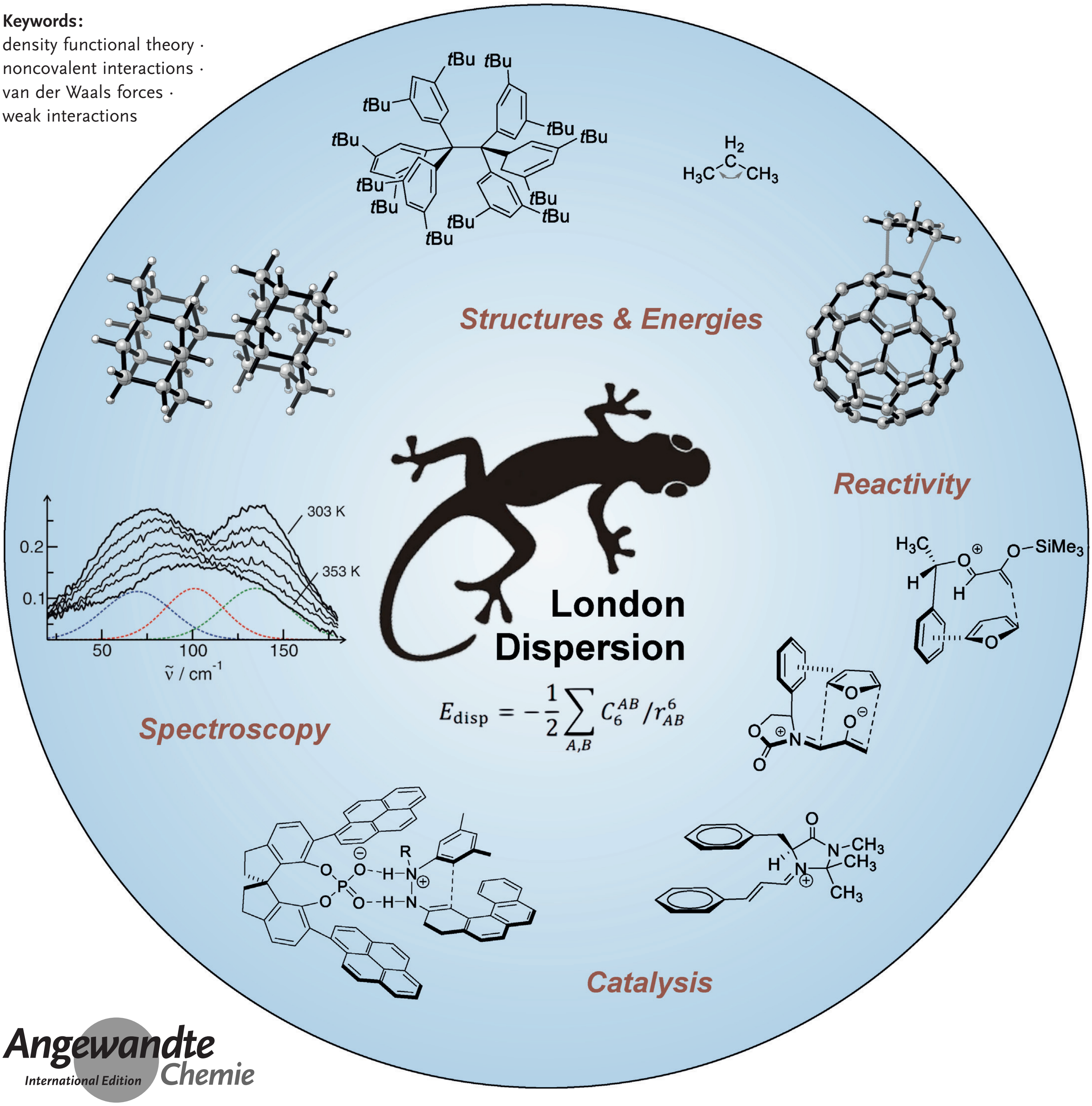
London Dispersion

International Edition: DOI: 10.1002/anie.201503476
German Edition: DOI: 10.1002/ange.201503476

London Dispersion in Molecular Chemistry—Reconsidering Steric Effects

*J. Philipp Wagner and Peter R. Schreiner**

Keywords:
density functional theory ·
noncovalent interactions ·
van der Waals forces ·
weak interactions



Angewandte International Edition Chemie

London dispersion, which constitutes the attractive part of the famous van der Waals potential, has long been underappreciated in molecular chemistry as an important element of structural stability, and thus affects chemical reactivity and catalysis. This negligence is due to the common notion that dispersion is weak, which is only true for one pair of interacting atoms. For increasingly larger structures, the overall dispersion contribution grows rapidly and can amount to tens of kcal mol^{-1}. This Review collects and emphasizes the importance of inter- and intramolecular dispersion for molecules consisting mostly of first row atoms. The synergy of experiment and theory has now reached a stage where dispersion effects can be examined in fine detail. This forces us to reconsider our perception of steric hindrance and stereoelectronic effects. The quantitation of dispersion energy donors will improve our ability to design sophisticated molecular structures and much better catalysts.

From the Contents

1. Introduction

1.1. London Dispersion—Unduly Underestimated

The Gecko can walk up a smooth glass window because of the adhesion in the millions of hydrophobic setae on its toes that undergo van der Waals (vdW) interactions with the surface;[1] this basic scientific discovery immediately led to a commercial product, the gecko tape. The attractive part of such vdW interactions is an electron correlation (quantum mechanical many-body) effect normally referred to as London dispersion. Its overwhelming role in the formation of condensed matter has been known since the pioneering contributions of van der Waals[2] and London, who related dispersion to spectroscopic properties, particularly the polarizability of the interacting partners.[3] Earlier studies in the 1920s by Debye assumed noble gas atoms with permanent multipole moments ("Debye's inductive effect"),[4] which proved, however, to be an unsatisfactory model. The first recognition of attractive interactions in gases and thereby deviating from hard-sphere models probably goes back to studies by Clausius on molecular motion and heat as early as 1857.[5] By comparing the transition from the liquid to the gaseous state, Clausius concluded that "… *ein Molecül von einem einzelnen anderen Molecül mit viel geringerer Kraft angezogen wird, als von der ganzen Menge von Molecülen …*" (two molecules are attracted much less by one another compared to when they are surrounded by many other molecules)." These findings were subsequently refined by Maxwell in his studies on the dynamical theory of gases[6] and by Boltzmann in his treatise on heat equilibria in gases.[7]

As the charge distribution of one molecule will be affected by the presence of another, the relationship to polarizability follows naturally,[8] and London described dispersion cunningly as "*[eine] kurzperiodische gegenseitige Störung der inneren Elektronenbewegung der Moleküle, welcher Beitrag bei den einfachsten nichtpolaren und auch noch bei schwach polaren Molekülen den Hauptbestandteil der Molekularattraktion darstellt*"[8b] (an interaction characterized by a short-period mutual perturbation of the inner electron motion of molecules whose magnitude is the major attractive contribution in the simplest nonpolar and also weakly polar molecules). As the estimation of the dispersion interactions was initially described through the optical dispersion formula ("*f*-values"), the somewhat confusing name stuck and is still employed by chemists.[9] To avoid confusion it is, therefore, sensible to use the term "London dispersion" (LD), which refers to the attractive term of the vdW equation.[8b] Curiously, London considered dispersion initially not as a quantum mechanical effect but rather a mechanistic model to describe medium- and long-range interactions of molecules in the gas phase.[8a] An important conclusion derived from the oscillating dipole model is that the induced dipoles from the alternating field result from the polarizability of the interatomic bonds and the presence of a propagating electromagnetic field, and the induced dipoles do not, in contrast to permanent dipoles, disappear at high temperatures.

In chemistry, dispersion helps rationalize the different boiling points of alkanes, the greater stability of branched over linear alkanes, the π-π attractive structures of graphite and graphenes, and the mutual attraction of σ-π systems. In this context, it is surprising that we typically introduce vdW interactions with the regular behavior of the boiling points of alkanes to explain their intermolecular attraction, but at the same time often forget to apply this concept intramolecularly, that is, to help understand the higher thermodynamic stability of branched over linear alkanes. In 1956, Pitzer and Catalano already pointed out that the differences in the isomerization energies of branched versus linear alkanes are due to intramolecular dispersion;[10] they arrived at this conclusion from their finding that the anomalous bond dissociation energies (BDEs) of the dihalogens are only in part due to

---

[*] M. Sc. J. P. Wagner, Prof. Dr. P. R. Schreiner
Institute of Organic Chemistry, Justus-Liebig University
Heinrich-Buff-Ring 58, 35392 Giessen (Germany)
E-mail: prs@uni-giessen.de

electron-pair (Pauli) repulsion and to a significant part to dispersion, which is largest for Cl_2 (by a factor of five over F_2, which is the least polarizable halogen!).[11] Although using a hard-sphere model (inclusion of LD would be termed a "soft-sphere model") and ignoring hybridization differences, Bartell pointed out in 1959 that "*intramolecular van der Waals forces may be even more important than effects of hybridization and conjugation or hyperconjugation in governing bond angles, bond distances, energies of isomerization and hydrogenation, and bending vibrations of molecules.*"[12] Indeed, Israelachvilli remarks in his textbook on intermolecular forces that, among the vdW forces, "*dispersion forces generally exceed dipole-dependent induction and orientation forces except for small highly polar molecules, such as water.*"[13] He illustrates this with a comparison of the hydrogen halides: although the dipole moment diminishes from HCl to HI, the dispersion energy contributions to the total interaction energy increase dramatically (as do the polarizabilities and boiling points).

It is important to recognize that dispersion interactions also are important control elements for reactivity and catalysis, in particular, for increasingly larger molecules, for which dispersion accumulates. Although many scientists know that dispersion interactions are important, they are often not considered in a quantitative fashion; generic names for less-well-defined quantities such as (often entropically driven) "hydrophobic"[14] or "fluorophobic interactions"[15] underline the difficulties many have with the use and description of dispersion forces. In this Review we emphasize the molecular aspect, as bulk dispersion is readily accounted for in condensed phases by utilizing statistical means.

In recent years it has become clear from various areas of theoretical and experimental chemistry that dispersion is more important than generally assumed. Part of this emerging interest comes from its R^{-6} dependence, thus making dispersion particularly relevant in large systems. Mainly driven by the theoretical analysis of the "failures" of density functional based electronic structure theory (DFT),[16] it has been recognized that dispersion is not only a long-range property but also has short- to medium-range components that affect the thermochemical properties of molecules.[17] An advantage of dispersion-corrected DFT is that dispersion can be switched "on and off", thereby allowing a discrimination from steric effects in condensed phases. This culminated in the concept of "dispersion energy donors" (DEDs),[18] which are polarizable moieties that can be used to stabilize unusual bonding situations or to control chemical reactivities. Recent findings challenge the predominant view that bulky groups in molecular structures are more likely considered repulsive rather than stabilizing. Recognizing that a delicate balance between attraction and repulsion can be quantitatively understood, the resulting approach may help establish new design principles.

One reason why dispersion interactions have mostly been overlooked is the common notion that they are weak (which is only true for one pair of interactions). For larger systems with many contacts, it is clear that dispersion is underrated relative to the importance of Coulomb interactions (Figure 1). Dispersion grows with the number of pairwise interactions between atoms and, thus, faster than the number of atoms.

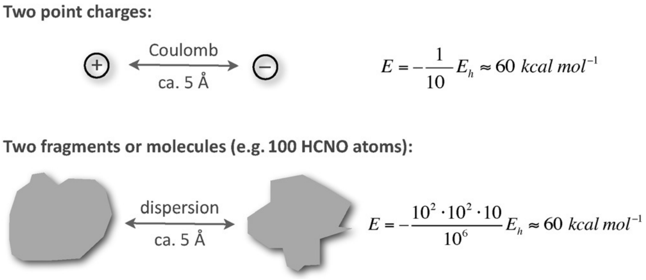
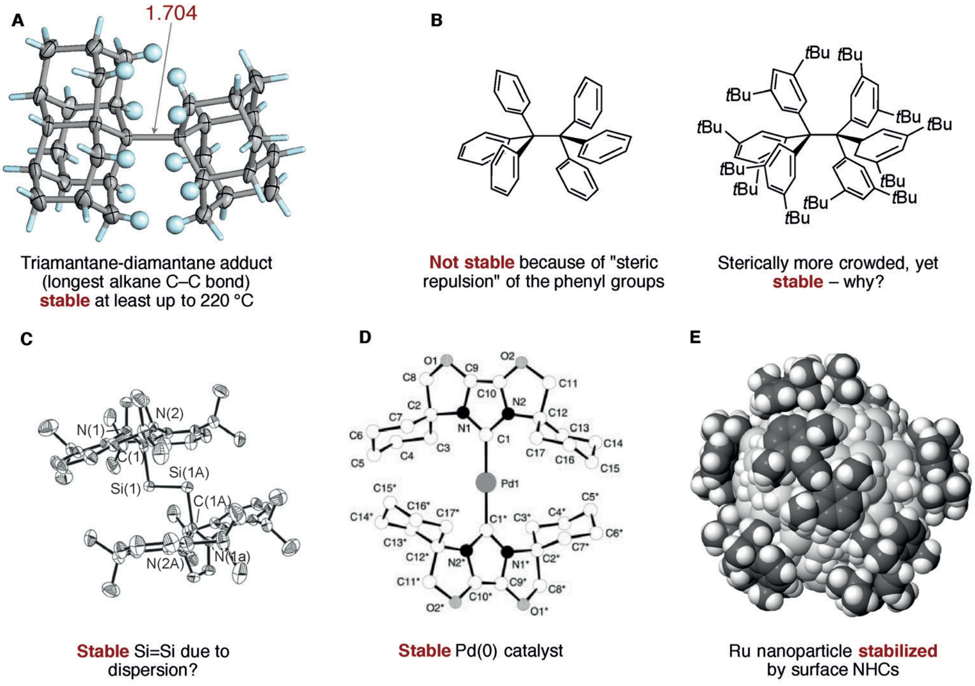


Figure 1. Comparison of electrostatic versus dispersion interactions in two systems that yield the same interaction energy (E): two point charges versus two dispersively interacting 100 atom fragments with 100 atoms at the same distance; the fragments are composed of C, H, N, O with an average dipole–dipole C_6 dispersion coefficient of about 10 E_h Bohr^6 (E_h = Hartree). Adapted from Ref. [19].

The idea of using stabilizing dispersion forces has already been used successfully to synthesize, for example, hydrocarbons with extremely long C–C bonds (A and B in Figure 2).[20] Equally, the stability of many unusual molecular fragments may be related to the interaction of DEDs in the periphery of the moiety under consideration. Pertinent examples include the preparation of, for example, "Si_2"

J. Philipp Wagner was born in 1988 in Giessen, where he also studied chemistry at the Justus-Liebig University (BSc 2010, MSc 2012). He is currently carrying out PhD research under the supervision of P. R. Schreiner. His research focuses on the effects of London dispersion and quantum mechanical tunneling in organic reactions. His work is supported by a doctoral fellowship of the Fonds der Chemischen Industrie.

Peter R. Schreiner (born 1965) studied and received his PhD (1994) in organic chemistry at the University of Erlangen-Nürnberg (Germany) with P. von R. Schleyer. Simultaneously, he obtained a PhD (1995) in Computational Chemistry from the University of Georgia, USA, with H. F. Schaefer. He was assistant professor in Göttingen and associate professor at the University of Georgia before accepting the chair of organic chemistry at the Justus-Liebig University Giessen (Germany) in 2002. In 2013 he became an elected member of the German National Academy of Science (Leopoldina) and in 2015 corresponding member of the NRW Academy of Sciences, Humanities, and Arts.



Triamantane-diamantane adduct
(longest alkane C–C bond)
stable at least up to 220 °C

Not stable because of "steric
repulsion" of the phenyl groups

Sterically more crowded, yet
stable – why?

Stable Si=Si due to
dispersion?

Stable Pd(0) catalyst

Ru nanoparticle **stabilized**
by surface NHCs

Figure 2. A) The longest alkane C–C bond achieved through strong dispersion stabilization along the H⋯H contact surfaces; B) crowding destabilizes experimentally unknown hexaphenylethane, while the more crowded all-*meta-tert*-butylhexaphenylethane can be crystallized; C–E) organic "skins" around central units; D) white C, black N, light gray O, dark gray Pd; E) NHC = N-heterocyclic carbene.

(Figure 2C), which may be considered possible only through the dispersion stabilization of the ancillary isopropyl groups,[21] although this has not yet been explicitly considered.[22] There is evidence that the properties of rather polar systems such as ionic liquids[23] or cationic complexes[24] are decisively influenced by dispersion. This is also true for the relative energies of conformers[25] and hydrogen-bonding networks,[26] the rotational barriers of alkanes[27] (protobranching[10,28]), 1,3-allyl strain,[29] the corset effect[30] and its extension,[31] and the widespread misconception that a *tert*-butyl group only acts repulsively.[32] However, many of these interactions have been explained in terms of alternative bonding models. This leaves much space for further refining our understanding of the chemical bond.[33]

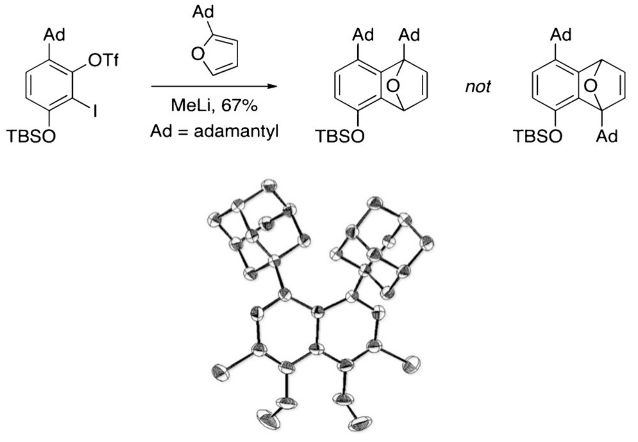
Experimentally, there is growing evidence that dispersion plays an essential role in what is considered to be a weak hydrogen bond: An aromatic alcohol interacts 35% more strongly with a cyclohexane than with a benzene molecule;[34] cyclohexane is actually more polarizable than benzene.[35] The interaction of alkanes with benzene correlates with their polarizability, but not with the number of CH-π contacts.[36]

Understanding the length scale for the transition from the continuum (where LD forces are dominant) to the atoms and the domain of covalent and ionic bonds is key for the development and understanding of materials, and for the exploration of the transition of the molecular to the material domain.[37]

Most practical chemistry occurs in condensed phases and one may argue that dispersion effects are attenuated in solution. Although intermolecular dispersion is diminished in solution,[38] dispersion will not vanish and its intramolecular component, as opposed to surface-proportional solvent effects, is retained locally—by how much is yet to be defined. In this context it is important to remember that biochemical systems have active sites that are not fully solvent accessible and, therefore, more resemble the gas phase rather than solution. LD clearly plays a decisive role in biology, for example, in the stability of the DNA helix,[39] in particular, for treating stacking interactions.[40]

The inclusion of LD is also important for reactivity and selectivity. One example is the reaction outlined in Scheme 1, which gives the apparently sterically more hindered product that is, perhaps, favored by dispersion attraction of the two large alkyl groups in the transition structure.[41] How can one use such findings to define optimal places and shapes for covalently linked DEDs in proximity to reactive centers (e.g. catalysts)?

The explicit consideration of LD in chemistry and the evaluation of its consequences on structure and reactivity is just at the beginning. We are now learning to appreciate the role this interaction plays in increasingly larger systems, which can be analyzed in much more detail than ever before through sophisticated experimental and theoretical techniques. This



Scheme 1. Selective formation of the supposedly more hindered product in a Diels–Alder reaction of an in situ generated 1,2-didehydrobenzene derivative, presumably as a result of dispersion interactions of the two adamantyl (Ad) groups. TBS = *tert*-butyldimethylsilyl, OTf = triflyl. Bottom: X-ray structure of the final product after acidification and methylation.

Review should provide an up to date status of the research and also alert chemists to the role that LD might play in their particular research area.

1.2. Structure of the Review

We focus on the importance and consequences of LD in molecular chemistry, in particular in structures containing elements of the first full period, for which there is now ample evidence for the overwhelming importance of LD. Dispersion is also important for the heavier elements, but has been examined even less; methods are only now being developed, for example, for metal binding, which typically involves many nonlocal electron correlation effects that make the dissection of the total energy into the various energy contributions more difficult.

We begin with a brief introduction to the theoretical framework on how LD is included in quantum chemical computations. The effects of dispersion interactions on chemical structures and reactivities follow, as well as a section on catalysis. We conclude with the spectroscopic signatures that help quantify dispersion interactions. Macroscopic materials, condensed phases, and supramolecular complexes are not our focus and are not being reviewed here.

This Review is not exhaustive but rather attempts to provide a current account of where we are in conceptually understanding LD in molecular chemistry. It is intended to provide an entry into the topic and a basis for discussion for its development. The reader is also referred to leading reviews on the theoretical[19,42] and experimental[43] elucidation of some aspects of LD.

2. Manifestations and Consequences

2.1. Theoretical Methods To Gauge Dispersion Effects

London's original formulation implies additivity, that is, the dispersion energy of three molecules can be computed from the sum of three pairwise interactions.[8a] This conclusion, however, is not substantiated with more sophisticated considerations of vdW interactions and they are not generally considered pairwise additive.[13] The force between two molecules is influenced by other surrounding molecules so that one cannot simply add all pairwise interactions to determine the total interaction energy of one molecule with the others. Although deviations from non-additivity may be small, it has to be taken into consideration for large molecules. Apart from oscillating dipoles, there are also higher-term interactions that are derived from oscillating quadrupoles or higher multipoles; although the associated R^{-8} value for quadrupoles still contributes to vdW minimum structures,[44] higher absolute exponents are less relevant.[45]

Traditionally, there are two ways to account for LD in intermolecular interactions: symmetry-adapted perturbation theory (SAPT)[46] and the supermolecular approach.[19] In SAPT, molecular fragments have to be predefined and the interaction energy is computed through a perturbation of the molecular complex. The advantage is that the energy is derived from physically meaningful components, which also facilitates qualitative interpretations. However, SAPT is only applicable if the interaction of the fragments is small and can be treated perturbatively, which excludes application to covalently linked fragments.[47] In the supermolecular approach, the energy is simply computed as the difference between the energy of the complex and the energies of the monomers [for size-extensive methods; Eq. (1)].

$$\Delta E = E(\mathrm{AB}) - E(\mathrm{A}) - E(\mathrm{B}) \tag{1}$$

However, this method is only straightforward for noncovalent complexes. To estimate the influence of dispersion on chemical reactions, it is instructive to compare levels of theory that explicitly account for dispersion with those that lack its description.[20a,48] Furthermore, energy decomposition analysis (EDA)[49] schemes can be used to quantify the contribution of LD to an interaction.[50] It can also be instructive to apply isodesmic reaction schemes to systems where a reference state is difficult to define.[20a] For example, protobranching stabilizations of *n*-alkanes can be estimated by applying bond-separation equations (see Scheme 2).[28]

Both wave function theory (WFT)[42d] and DFT[42b] can be employed for the evaluation of dispersion interactions. However, for both methods, attention has to be paid to the so-called basis set superposition error (BSSE).[51] This error occurs when two molecular fragments approach each other and one monomer "borrows" basis functions from the other to lower its energy. This is pronounced for small basis sets and leads to an over-stabilization of the complex. A counterpoise correction can be applied for noncovalently linked fragments, but this is not straightforward for intramolecular interactions.[52] Thus, it is recommendable to use large basis sets and, especially for WFT, to utilize systematically converging basis sets[53] (augmented with diffuse functions)[54] and apply complete basis set extrapolation (CBS) schemes.[42a]

WFT is, in principle, able to yield high-quality properties and energies, but is typically much more time-consuming than DFT. It is also possible to crudely estimate the amount of dispersion contributing to the binding of an intermolecular complex by comparing correlated levels to the Hartree–Fock (HF) method, as LD is a consequence of the correlated electron movement. Chemical accuracy can be obtained by employing coupled-cluster theory[55] with iteratively included single and double excitations and perturbatively treated triple excitations, namely CCSD(T),[56] extrapolated to the basis set limit, for example, with a focal point analysis.[57] One can estimate the second-order Møller–Plesset (MP2) correlation energy with a power law[58] to the basis set limit and include higher order correlation effects using a small basis set [Eq. (2)].

$$\Delta\mathrm{CCSD(T)} = (\Delta E^{\mathrm{CCSD(T)}} - \Delta E^{\mathrm{MP2}})_{\text{small basis}} \tag{2}$$

This can be done if one assumes that MP2 and CCSD(T) converge similarly with respect to the basis set. It saves time to use MP2 in the resolution of the identity approximation (RI, density fitting).[59] Here, the two-electron integrals are approximated within an auxiliary basis set almost without loss of accuracy.

Cheaper WFT approaches to describe LD are also available, however, at the expense of accuracy. Large basis set second order Møller–Plesset perturbation theory yields accurate energies of saturated and hydrogen-bonded systems, and coupled-cluster corrections tend to be small.[60] Unfortunately, the method fails alarmingly for interactions of unsaturated systems such as the benzene dimer.[60a,61] Some deficiencies can be corrected by scaling the spin components of the correlation energy (SCS-MP2).[62] The idea is that in HF theory same-spin electron pairs are already correlated, while opposite spin pairs are not. Thus, the individual spin components can be scaled to match high-level benchmark data to improve overall accuracy. SCS-MP2 has been applied extensively to noncovalent complexes, for which it was originally not intended. As expected, stacking interactions are well accounted for, but saturated bonds and hydrogen-bonding interactions are underestimated. Overall, there is an improvement in the performance relative to MP2.[63] Generally speaking, MP2 overestimates dispersion, while SCS-MP2 underestimates it systematically by 10–20 % relative to coupled-cluster results.[62] Based on the SCS idea, an entire "zoo" of such methods[64] has been developed, of which the SCS-CCSD[65] method proved quite robust.

There are two flavors of WFT that have been emerging rapidly: explicitly correlated WFTs,[66] which converge faster to the basis set limit, and techniques that truncate the virtual orbital space. Neese et al. revived the localized pair natural orbital approach, noticing that some virtual orbitals are more important to the correlation energy than others.[67]

In general, DFT computations are much cheaper than those performed with correlated WFT methods and thus are also applicable to large systems. However, 20 years ago it had already been noticed that almost all standard approximations of DFT fail to describe dispersion interactions.[16e,f,68] The impressive success of the B3LYP/6-31G(d) level of theory could be explained retrospectively to rely on error compensation that cancels the lack of dispersion by pronounced BSSE.[69] The failure of standard DFT is not surprising, as the energy is approximated on the basis of local quantities of the local electron density or the reduced density gradient in GGA functionals, while LD is a long-range interaction. In the last few years huge efforts have been made to include LD into DFT.[42] Several strategies exist that have been grouped by Klimeš and Michaelides into several "stairways to heaven"[70] in analogy to Perdew's "Jacob's ladder" of DFT.[71] At step zero are functionals that lack the correct description of the r^{-6} dependence in the long-range potential. Examples are the extensively parameterized functionals of the Minnesota family developed by Truhlar and co-workers that were specially trained for noncovalent interactions.[72] Despite this unphysical property, these functionals often show superior performance at the equilibrium geometry. For example, the methods are able to determine the isomerization energy of tetramethylbutane to *n*-octane very accurately, while most standard density functionals do not even get the sign of the energy change right.[16a,b,73] They are also able to accurately predict the energies of nucleic acid dimers.[74]

The next rung corresponds to methods that treat the dispersion energy based on simple C_6 corrections. The dispersion energy is added a posteriori to the DFT energy based on atom-pairwise interactions over all atom pairs A and B [Eq. (3)].

$$E_{\mathrm{Disp}} = -\frac{1}{2}\sum\nolimits_{\mathrm{A,B}} C_6^{\mathrm{AB}}/R_{\mathrm{AB}}^6 \tag{3}$$

This idea originally emanates from attempts to correct HF theory[75] and was brought to DFT later.[76] As a consequence of the semiempirical character of the C_6 correction, it can be regarded as a QM/MM method. The most prominent implementations are Grimme's original D correction[77] and the improved D2 version.[78] The C_6-based methods rely on damping functions that are equal to unity at long distances but dampen the dispersion interaction to a finite value at short distances. This is necessary to avoid the double counting of correlation effects at short distances, at which standard DFT works well, and also to avoid instabilities arising from unphysically large dispersion interactions. If the interaction is damped to zero, very short noncovalent contacts as, for example, in hexabromoethane are elongated upon adding dispersion. This counterintuitive behavior can be corrected using a Becke–Johnson (BJ) damping function that scales the dispersion contribution to a constant value at the united atom limit.[79] As the dispersion energy corresponds to the correlation energy within the random-phase appoximation (RPA), this approach is also quite suitable for estimating dispersion energy contributions, and it can be used to devise improved damping functions.[80]

Step two of the ladder is Grimme's D3 version of the C_6-based corrections.[81] It additionally includes C_8 coefficients that account for the shorter range part of the potential. More importantly, environment-dependent C_6 values were introduced to account for the chemical nature of the interacting atoms. This is, for example, necessary to describe σ- and π-stacking correctly.[82] Whereas the appropriate C_6 coefficient is chosen for the D3 correction on the basis of the number of neighboring atoms, the vdW(TS) correction of Tkatchenko and Scheffler compares the volume of an atom in a molecule to a (free atom) reference state and scales the C_6 coefficient on that basis.[83] The third method is the one of Becke and Johnson that also comes with the highest computational expense.[84]

On step three of the ladder are methods that compute the dispersion interactions directly from the electron density. This approach grants some ab initio character to these density functionals, as no external input is needed for the determination of the C_6 coefficients. These functionals are called vdW density functionals (vdW-DF)[85] because they add a nonlocal term for the correlation energy to a local correlation functional. Vydrov and van Voorhis noticed that the long-range correlation was overestimated by vdW-DF[86] and suggested the VV10[87] functional, which has proven very successful. It has been shown that VV10 performs comparably well with D3-corrected (hybrid) GGA density functionals, which are somewhat less costly.[88]

Arguably, the currently final step of the ladder unites diverse approaches, of which the most popular is maybe double-hybrid DFT.[89] In the first double-hybrid density functional, B2-PLYP,[90] a certain amount of the correlation functional is replaced by a correlation energy computed with the aid of virtual orbitals. This makes the computations very expensive and somehow violates the original spirit of "occupied orbital only" DFT.[91]

A generally useful tool to visualize dispersion interactions developed recently is noncovalent interaction (NCI) analysis.[92] The method is closely related to Bader's quantum theory of atoms in molecules (QTAIM),[93] which has been adapted to be specific to the application of noncovalent interactions. The method investigates the electron density regions in which the reduced density gradient vanishes at low electron densities. Repulsive and attractive interactions can be discerned by the sign of the second eigenvalue of the Hessian of the density. In contrast to QTAIM, the gradient does not have to be exactly zero, which has proven useful for the identification of intramolecular hydrogen bonds.[94] NCIs can be displayed in three dimensions, where dispersive attractions are usually indicated by green surfaces.[95,96]

Finally, the analysis of the wave function with respect to determining the relative weight of dispersion interactions can also be accomplished using valence bond theory, which reveals charge-transfer interactions between interacting molecules or moieties, very much in the spirit of oscillating dipoles in London's original formulation.[97] Although this approach works well for small molecules, recovering the interaction energies of, for example, large alkane fragments requires recoupling of the primarily interacting C−H⋯H−C bonds to the electrons of larger parts of the participating molecules. As a consequence, there is a dependence of the C−H⋯H−C interaction strength and the rest of the molecular structure in terms of the size of the remaining moieties connected to the C−H bonds: counterintuitively, steric hindrance can lead to increased interaction (see Section 2.2).[98] Similarly, electron decomposition analysis (EDA) reveals the secondary but important role of charge transfer in these types of attractive H⋯H contacts.[99]

It seems that the theoretical arsenal is now available to evaluate the relative importance of LD in molecular chemistry. The option of being able to switch the corrections on and off as well as the availability of highly accurate methods such as (domain-based) local coupled-cluster implementations and linear scaling approaches[100] will help in deciphering the molecular details and consequences of including dispersion in increasingly larger structures.

2.2. Consequences for Structures and Energies: Reconsidering Steric Effects

The alkanes and alkyl groups in heteroatomic and other hydrocarbon structures are the ideal testing ground to determine dispersion effects. This is not to say that dispersion is not present in polar and charged systems, but the alkanes and alkyl groups lack intrinsic polarization so that their structures and energies can readily be separated into covalent and vdW contributions. Insights gained from understanding these simple building blocks form the basis of our rationalization of molecular interactions in chemistry and the life sciences.

The methane dimer provides a lower bound energy value for the magnitude of alkane–alkane dispersion interactions. Unsurprisingly, the methane dimer dissociates exothermically at the HF level and with dispersion-uncorrected DFT, even with large basis sets.[101] As the experimental dimerization energy amounts to about 0.5 kcal mol^{-1}[102] (high levels of ab initio theory reproduce this value very well),[60a] one must conclude that a single methyl–methyl or even methylene–methylene (depending on orientation) interaction accounts for about 0.5 kcal mol^{-1} of attraction in dispersion. As the alkanes or interacting alkyl moieties get larger, this interaction energy increases significantly. Incidentally, the interaction energy of the cyclohexane dimer is about 2.7 kcal mol^{-1} at CCSD(T)/CBS,[103] which is close to a linear extrapolation from the interaction energy of the methane dimer. The interaction topologies (the number of H⋯H contacts and their orientation) of the alkane surfaces facing each other, as well as the size of the entire hydrocarbon, also strongly affect the binding energies; polyhedral and branched alkanes tend to have higher interaction energies than linear alkanes.[98] For example, depending on the approach geometry, with different numbers of mutually facing C−H⋯H−C contacts, the interaction energy of two adamantane molecules varies in the range of 0.5 to 1.4 kcal mol^{-1}. Even more striking, this interaction also depends on the overall molecular size (which could be related to polarizability); for example, the cubane and octahedrane dimers have interaction energies of 2.0 and 2.5 kcal mol^{-1}, respectively.[98] Most surprising is the effect when comparing the methane and isobutane dimers with a 1:1 C−H⋯H−C contact topology (for fair comparison): the interaction energy for the isobutane dimer is about six times as large (0.7 kcal mol^{-1}) as that of the methane dimer in this topology (0.12 kcal mol^{-1}), and the H⋯H distance shortens from 2.5 Å in the methane dimer to 2.1 Å in the isobutane dimer, despite a formal increase in steric hindrance. In line with this finding, the isobutane dimer has a dissociation energy about twice as large as that of the *n*-butane dimer, despite comparable polarizabilities.

π-π Interactions are invoked much more often than σ-σ interactions in rationalizing structural stabilities. This is surprising in view of the fact that the most favorable *n*-pentane dimer is bound by 3.6 kcal mol^{-1},[104] which significantly exceeds the association energy of the benzene dimer (2.7 kcal mol^{-1}).[60a] This seems counterintuitive considering the much higher boiling point of benzene (which should be roughly related to the enthalpy of vaporization by Trouton's rule), but relates to the conformational flexibility of the alkane: the *gauche* conformer is the most abundant at room temperature but it cannot align nearly as well as the all-*trans* conformer.[105] In contrast, rigid alkanes, similar to the polyhedranes, show extraordinarily high melting points and association energies.[98]

Examination of even larger all-*chair* cyclohexane-based alkane dimers ("graphanes", Figure 3) and comparisons with aryl–aryl (π-π) dimers brought to the fore that π-π and σ-σ interactions are equally important (not equal),[106] with the π-π interactions growing more quickly with an increasing size

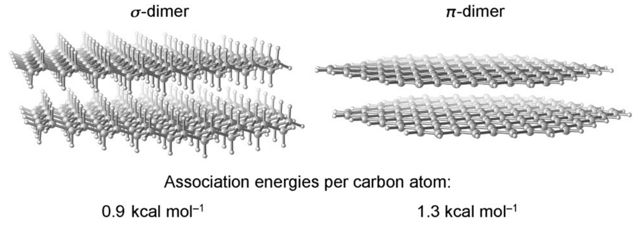


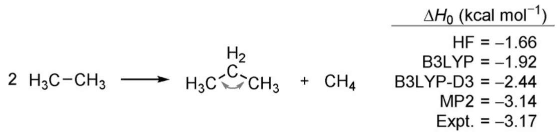
Figure 3. Exemplary depictions of large regular σ-σ and π-π dimers of comparable size:[106] [121]graphane and [130]graphene and their association energies per carbon atom at the CCSD(T) level of theory.[107]

of the interacting groups.[82,107] This general conclusion was confirmed independently[107] and refined, whereby σ-σ and σ-π interactions are considered local but π-π stacking is inherently delocalized, thereby giving rise to a non-additive effect.[96] Secondly, the interactions are accompanied by an intuitively understandable charge-transfer contribution that further shortens H···H contact distances and amounts to about 15% of the total interaction energy.[108]

Nature seems to be employing these principles in building membranes from either long-chain fatty acids, or, when required from more rigid steroid skeletons, even all-*trans*-fused cyclobutanes ([*n*]ladderanes[109]) that provide exceptionally dense cell walls for some bacteria that have to resist oxidative stress.[60c] Although the assembly of such strained polycycles requires quite some energy, their association leads to dispersion-dominated interaction energies that are significantly higher than even longer straight-chain fatty acids. Clearly, much can be learned from studying the details of the intermolecular C−H···H−C (σ-σ) bond that has been neglected relative to the recognized importance of the π-π[110] (for a critical view see Ref. [111]) and σ-π bonds,[112] despite the fact that it is of comparable magnitude.

The intramolecular C−H···H−C case is even less appreciated. Measures for the relevance of this interaction between hydrogen atoms at the proper (attractive) vdW distance come from a variety of conformational equilibria and structures that are far more stable than anticipated on the basis of the presence of large groups which are viewed as sterically encumbered.[43] For example, it has been known for more than 50 years that 1-propyl chloride[113] and fluoride[114] prefer *gauche* conformations, but this may also be rationalized on the basis of electrostatics.

As mentioned in the introduction, Pitzer and Catalano rationalized the higher stability of branched over linear alkanes through their higher intramolecular dispersion energy based on simple calculations utilizing London's original dispersion equation.[10] About ten years ago the problem appeared again in the chemical literature, when it was noticed that common DFT implementations were unable to reproduce the thermochemistry of alkane isomerizations[16a] and the relative energy differences of other hydrocarbon isomers.[16b,115] For example, many common density functionals produce erroneous results—even the sign—for the isomerization of *n*-octane to 2,2,3,3-tetramethylbutane,[16a] with M05-2X being an exception.[116] Schleyer and co-workers generalized the problem by applying DFT to bond separation equations as shown in Scheme 2.



Scheme 2. Isodesmic bond separation equations to evaluate the protobranching stabilization of propane. A cc-pVTZ basis set was employed.[28]

Standard DFT also fails badly for such isodesmic reactions and errors accumulate with increasing molecular size.[117] Schleyer and co-workers concluded that 1,3-alkyl contacts must be attractive in nature, and termed these interactions "protobranching" (indicated with an arrow in Scheme 2).[28] They chose this name because protobranching appears first in the kinked geometry of propane and helps rationalize why branched alkanes are more stable than linear ones. Although protobranching has been heavily criticized,[118] the importance of electron correlation clearly suggests attractive interactions of 1,3-alkyl groups. In 1958, Allen already speculated about such an attraction of "next-nearest neighbors" in linear alkanes to explain the dependence of the carbon–carbon bond strength on the chain length of linear alkanes.[119] Although Allen made LD solely responsible for this anomaly, MP2 computations with localized molecular orbitals revealed that correlations at a medium-range length scale are largely responsible for branching[78] and the protobranching effect.[120] Almost the entire difference in the correlation energy for the equation depicted in Scheme 2 comes from interpair correlations of C−H bonds in the two methyl groups, corresponding to a 1,3-interaction.[120] Of course, 1,3-alkyl contacts are absent in methane and ethane, which is why these two simple hydrocarbons cannot profit from protobranching. However, adding a dispersion correction to the DFT levels does not fully correct the energy difference. With the most modern DFT-D3 approaches, an error of about 30% remains, which is truly a medium-range correlation effect, in contrast to the rather long-range LD.[121]

More striking examples of intramolecular attraction come from the equilibrium position of the conformers of 1,3,5-tribromo-2,4,6-trineopentylbenzenes[122] and 1,4- versus 1,6-di-*tert*-butylcyclooctatetraene double bond shift isomers (Figure 4).[123] Dynamic NMR measurements revealed that the all-*cis* conformation of trineopentylbenzene is favored owing to an attractive interaction of the *tert*-butyl groups in fluorobenzene; in other solvents, this preference is reduced or even inverted (e.g. in highly polarizable CS_2). Similarly, 1,6-di-*tert*-butylcyclooctatetraene, which is seemingly sterically more encumbered, is preferred (in $CDCl_3$) over the 1,4 isomer. The authors also argue that this is due to dispersive attraction in the 1,6 case.[123,124] These findings are indirectly supported by the notion that molecular mechanics approaches require attractive (electronic) terms to account for the observed equilibria.[125]

If one arrives at the conclusion that intramolecular dispersion interactions can decisively stabilize molecules that otherwise have labile bonds, then an extension of this line of thought is to use this "dispersion glue" around reactive

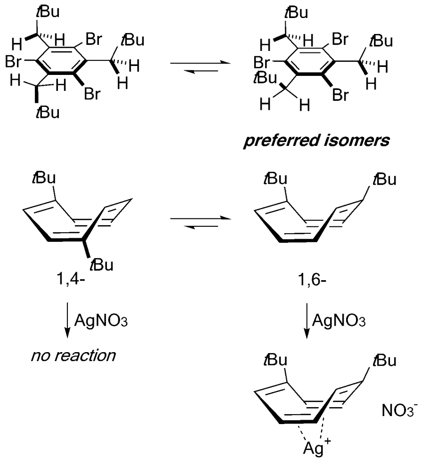


Figure 4. Equilibrium dynamic NMR measurements of tribromobenzene and cyclooctatetraene substituted with neopentyl and *tert*-butyl groups, respectively: the "more crowded" conformer is preferred and reacts preferentially.

molecules (not just bonds) to stabilize them to the degree that they can be isolated and characterized. A case in point is the so-called "corset effect", which was coined to visualize the stabilizing effect of the *tert*-butyl groups in tetra-*tert*-butyltetrahedrane.[30] While the nature of this stabilization was originally not elaborated, the notion of "maximum mutual separation" (of the *tert*-butyl groups) implies steric hindrance imposed by the large substituents. The computed homodesmotic energy comparison (Figure 5)[20a] indicates that this can only partly be true, as there must be a significant dispersion component, that is, a stabilizing contribution that favors the putative "steric crowding" in tetra-*tert*-butyltetrahedrane relative to di-*tert*-butyltetrahedrane with only two *tert*-butyl groups. This is indeed akin to a "corset" around an otherwise unstable (or unknown) molecule (parent tetrahedrane).

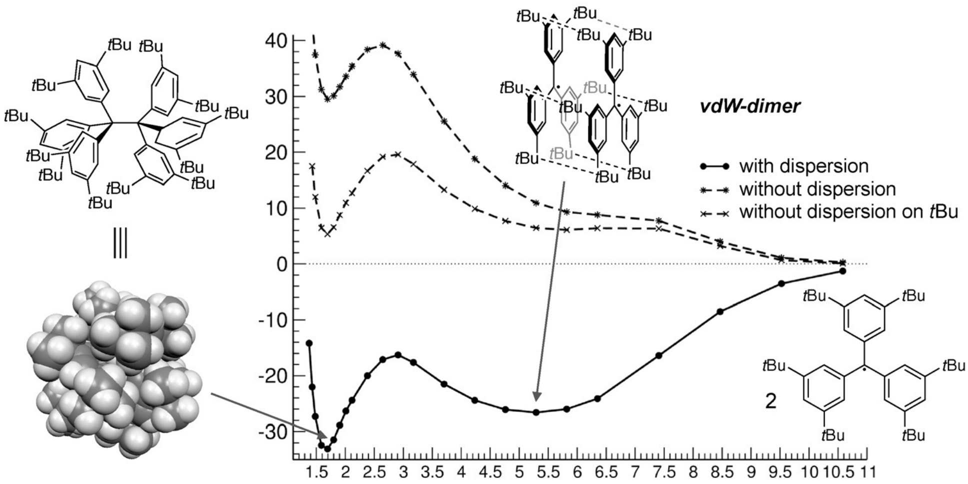


Figure 6. Computed (TPSS-D3/TZV2P//PBE-D3/TZVP) potential-energy hypersurface for the dissociation of the central C–C bond of all-*meta-tert*-butylhexaphenylethane (left, also as a vdW surface model) with and without dispersion correction, and with dispersion "switched off" only for the *tert*-butyl groups.[135] Note, the second isomer in the middle of the full dispersion curve: a bond length isomer bound through the *tert*-butyl groups only.

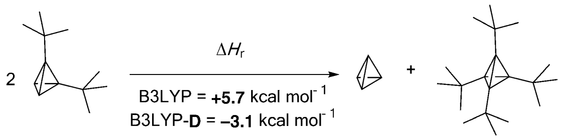


Figure 5. Homodesmotic equation to evaluate the dispersion stabilization of tetra-*tert*-butyltetrahedrane computed at the B3LYP/6-31G(d,p) level without and with dispersion (-D) correction.

This conclusion leads to the generic concept of using a corset-like dispersion shell to stabilize labile parts inside this shell (Figure 2 C–E). This principle was perhaps exercised and recognized for the first time in the crystal structure of Sc(III)trishexamethyldisilylamide, in which "… *the metal ion is squeezed out by a symmetrical contraction arising as a result of intramolecular-interligand van der Waals attractions.*"[126]

The attractive component of *tert*-butyl groups in intramolecular bonding situations is vividly demonstrated by the so-called "hexaphenylethane riddle":[127] The fact that the addition of "sterically demanding" *tert*-butyl groups to hitherto unrealized structures such as hexaphenylethane (HPE, Figure 6)—deemed "*too sterically crowded to be synthetically accessible*"[128]—even allows its crystallization![129] The argument put forward in this case is indicative of our conceptually incomplete understanding of "steric demand" (as a balance of repulsive and attractive forces), namely, that steric congestion has been made solely responsible for the thermodynamic instability of HPE[128,130] in the first place, and all synthetic approaches to prepare this seemingly simple molecule failed. Computations indicate that its BDE is only about 17 kcal mol^{-1}.[131] It was not recognized until 1968 that Gomberg's[132] triphenylmethyl radical does not dimerize to give HPE,[127] but instead gives (4-(diphenylmethylene)cyclohexa-2,5-dien-1-yl)methanetriyltribenzene}.[133] The generic argument for the instabilities of HPE derivatives is steric repulsion of the phenyl groups, despite their favorable mutual local T-shaped benzene dimer type orientations. However, the sterically much more crowded all-*meta-tert*-butyl derivative (Figure 6) is stable in the solid state (m.p. = 214 °C) in an inert atmosphere and its crystal structure has been resolved[129] (no other spectral data are known, though).

How can the derivative of a molecule that dissociates as a result of steric hindrance become stable by increasing the steric bulk? This question was answered by demonstrating that the all-*meta-tert*-butyl derivative is held together by extraordinarily strong LD interactions that turn dimerization into an exothermic process because of the many favorable CH···HC contacts of the *tert*-butyl groups. It is in this context instructive to reread Mislow's beautiful structural analysis paper of 1981 and muse about his statement that “*the tert-butyl groups have no special effect on the bonding parameters of* [*all-meta-tert*-butyl HPE]”.[130a] This is in line with common expectations, but does not provide a rationale for the stability of all-*meta-tert*-butyl HPE. The depiction of the vdW surface of the molecule (Figure 6) suggests that it is indeed a sterically crowded molecule and also that the *tert*-butyl groups tightly fit within reasonable vdW distances. The electronic effect of the *tert*-butyl groups is expected to be small because of their large distance to the central C–C bond; if anything, they should drive the dissociation to the Gomberg-type radicals through electron donation. The argument that the radicals could not dimerize to the McBride-type product may be correct, but it does not hamper the all-*para-tert*-butyl HPE derivative, which dissociates into persistent radicals.[134]

The dispersion correction to the dissociation energy of all-*meta-tert*-butyl HPE is huge: Without dispersion, it is thermodynamically unstable, with a negative dissociation energy (D_e) of -26.4 kcal mol^{-1}, which is about 10 kcal mol^{-1} even more exothermic than HPE itself. At face value, and without considering the stabilizing effect of the mutual C–H···H–C attraction, this would be perfectly in line with an increased steric demand and the greater instability of the *tert*-butyl-substituted derivative. The inclusion of dispersion provides a stabilization of 26.8 kcal mol^{-1}, which leads to an overall positive (endothermic dissociation) D_e value of $+10.1$ kcal mol^{-1}. Thus, the dispersion stabilization is as large as 61.6 kcal mol^{-1}, and the DFT-D3-computed D_e value of 35.2 kcal mol^{-1} is consistent with a thermally labile molecule that slowly dissociates at room temperature in solution.[129] Solvent effects using standard solvation models correct the D_e value by about 10–12 kcal mol^{-1} in favor of the radicals, which is still about an order of magnitude smaller than the intramolecular dispersion effect of about 60 kcal mol^{-1}.

The dissociation curve for the central C–C bond is also affected by structural dispersion effects, which are counterbalanced by Pauli repulsion (Figure 6): The curve exhibits two minima at C–C distances of 1.67 and 5.28 Å that are connected by a transition structure with C–C = 2.87 Å. The second higher-lying minimum is the vdW dimer and is devoid of a covalent central C–C bond. As the two minima lie in deep potential energy wells of -33.2 and -26.6 kcal mol^{-1}, respectively, both should be identifiable experimentally. Note that the vdW dimer disappears when the dispersion corrections are completely “switched off” and it is only faintly visible when the dispersion contributions are turned off for the *tert*-butyl groups only. Hence, the origin of attraction goes back to the *tert*-butyl groups, which stabilize the molecule against dissociation. Furthermore, the total energy is always higher than that of the free radicals, which emphasizes the importance of dispersion.

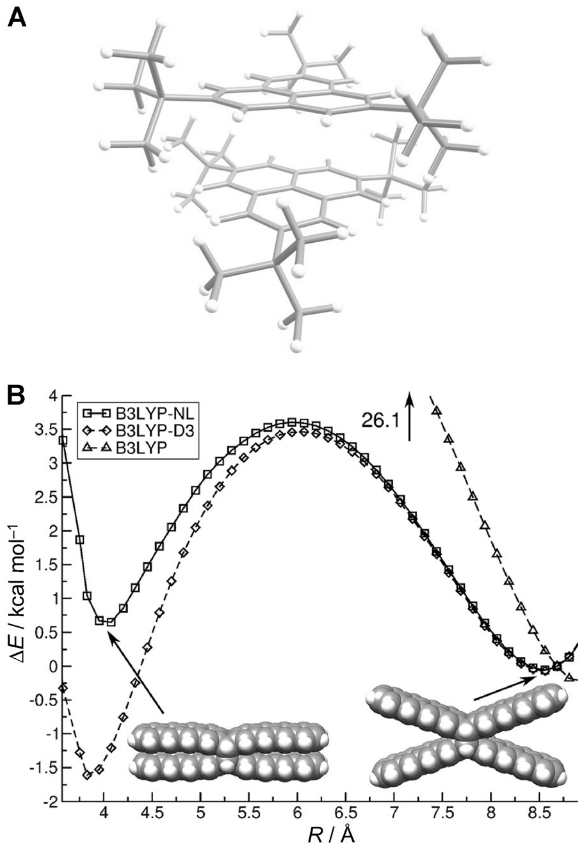


Figure 7. A) Structure (B3LYP-D3/cc-pVDZ) of biphenalenyl: the role of the *tert*-butyl groups has not been examined in detail. B) Dispersion corrections (-NL or -D3; basis set: def2-QZVP) are needed to describe the structure of the nonacene dimer correctly. *R* refers to the distances of the centers of the outermost rings. Adapted from Ref. [143].

Closely related to the HPE derivatives in terms of being composed of two tripodal radicals that may dimerize, are the biphenalenyl systems (Figure 7 A).[136] Although these have been examined and described in much detail, the omnipresent *tert*-butyl groups are typically interpreted as avoiding dimerization: “*The molecule forms a dimeric pair in a staggered arrangement of tert-butyl groups to avoid steric repulsion*”.[136] The question whether the *tert*-butyl groups may actually stabilize thermodynamically against dissociation into the free radicals has been addressed only in part.[137] The so-called “pancake-bonded” dimer with atomic distances well below the sum of their vdW radii has been identified by cold-spray ionization mass spectrometry and NMR spectroscopy, and is viewed to arise solely from aromatic π-π overlap.[138] In considering the arguments put forward in the previous sections and taking into consideration that the unsubstituted phenalenyl radical forms a σ-C–C-bonded dimer on its ring periphery (and not in the center),[139] it is unsurprising that dispersion contributions were found to have a large effect on the formation of the dimer: “*the dispersion component, which is not accounted at all in Hartree–Fock calculations, and improperly accounted in B3LYP calculations, is essential for the stability of the dimer* …”.[140] Although the authors found a dispersion energy correction of 32 kcal mol^{-1}, it was not related to the presence of the *tert*-butyl groups, but was instead assigned to be an essential feature of the π-π bonding arrangement, also referred to as "*nonspecific vdW contributions*" in another critical theoretical analysis of this system.[137a]

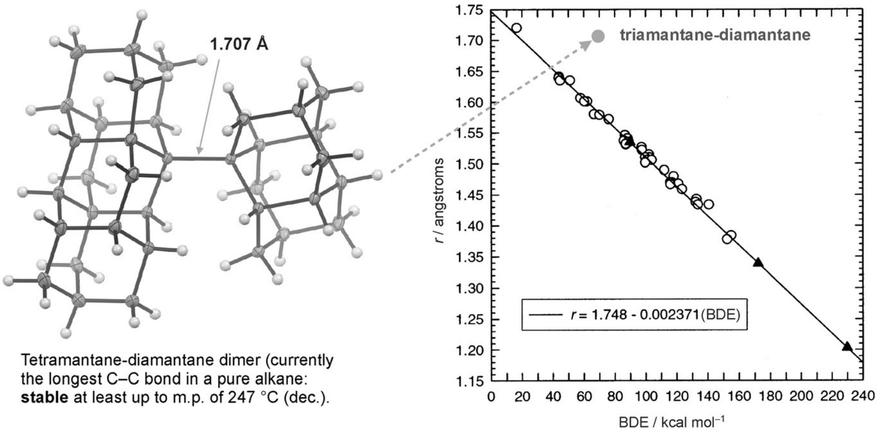


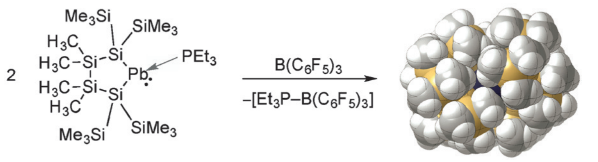
Figure 8. Single-crystal X-ray structure of the singly bonded tetramantane–diamantane adduct with currently the longest alkane C–C bond; however, the molecule is exceptionally thermally stable. The graph on the right is adapted from Ref. [148] with permission. Copyright (2003) American Chemical Society.

Dispersion is also responsible for the intramolecular stabilization of flexible molecules such as acene dimers. Acenes larger than pentacene are highly reactive and tend to dimerize; heptacene is already too unstable to be isolable.[141] Higher acenes can be prepared and characterized by using cryogenic matrix isolation techniques.[141,142] The extended π-systems result in strong intramolecular dispersion interactions that lead to conformational isomerism with a "butterfly-like" dispersion-stabilized structure. This is probably first the case for the nonacene σ,σ-dimer (Figure 7B), and it is difficult for standard computational techniques to handle these in a balanced fashion.[143] As the acenes get longer, the pairwise additive dispersion interactions of the mutually aligned acene moieties will at some point overcome the energy penalty associated with ring bending and Pauli repulsion, and the stacked conformer should become more favorable. As shown in Section 2.5 (see Figure 16), this is quite analogous to the folding of long *n*-alkane chains,[144] where the folded structure is energetically favored after a certain chain length. Note that the MP2 method performs poorly for such π-stacked aromatic systems relative to high-level benchmarks, and DFT approaches including pairwise additive dispersion corrections (-NL or -D3; see above) are a better choice. Thus, the stacked structure for the nonacene dimer is slightly more favorable than the open structure, at least in the gas phase and by the B3LYP-D3 approach (Figure 7B); the fully optimized geometry shows that the acene moieties are somewhat offset from the maximum symmetry (D_2).[143] However, the computations also show that solvation (in benzene) favors the open conformer and currently one can only speculate about the situation in the solid state.

A fascinating example of the decisive strength of dispersion interactions comes from the extraordinary stability of singly bonded diamondoid dimers (Figure 8).[20] Diamondoids are nanometer-sized diamond-like cage hydrocarbons consisting of face-fused adamantane building blocks.[145] The construction of hydrocarbons with very long C–C bonds is generally accomplished through the introduction of sterically demanding groups.[146] Although not based on physical laws,[147] there are empirical bond distance/bond strength relationships[148] that typically work exceptionally well for hydrocarbons: short bonds are considered stronger than long bonds,[149] as outlined by Pauling in 1960[150] and also recently.[148] The preparation of a series of coupled diamondoid (hetero)dimers revealed highly sterically congested structures with exceptionally long central C–C bonds of up to 1.707 Å in 2-(1-diamantyl)[121]tetramantane (Figure 8, left), the longest C–C bond in a pure alkane reported to date (longer C–C bond lengths of up to 1.78 Å have been reported for heteroatom-containing structures[151]). The most sterically crowded alkanes prepared previously display C–C bonds of up to 1.65 Å,[152] and these are considered thermally labile with short half-lives at elevated temperatures. Even more sterically crowed alkanes were deemed not possible, because the BDEs for C–C bonds longer than 1.65 Å were empirically estimated to be only around 41 kcal mol^{-1} (Figure 8, right).[146,148]

However, the diamondoid dimers are thermally highly stable even at temperatures well above 200 °C, in stark contrast to what is expected from C–C bond length/bond strength relationships (Figure 8, right): they are well "off the line!" The extraordinary stabilization apparently arises from numerous intramolecular dispersion interactions of the H-terminated diamond-like surfaces and the fact that the radicals formed from C–C bond dissociation are structurally very similar to the hydrocarbon moiety in the undissociated starting materials.[20a,153] Radical-stabilizing effects are, thus, minimized. Unsurprisingly, only functionals accounting or corrected for dispersion are able to reproduce the experimental geometries of these structures. The dispersion contributions were estimated to exceed 30 kcal mol^{-1},[20] that is, about one third of a covalent C–C bond.

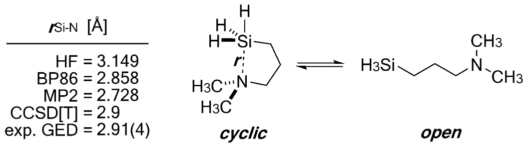
Inorganic structures also often rely on the stabilizing presence of dispersion interactions of surrounding hydrocarbon moieties. We will briefly mention only two examples. For example, the reaction of a triethylphosphine-coordinated cyclic disilylated plumbylene (Scheme 3) with the strong Lewis acid $B(C_6F_5)_3$ leads to abstraction of the phosphine ligand and formation of the corresponding plumbylene dimer.[154] Surprisingly, the lead atoms in the dimer have distorted trigonal and pyramidal coordination, which indicates that the two lead atoms are connected with just a single Pb–Pb instead of a (formal) double bond. This finding is in line with an NBO analysis, and the Wiberg bond index is smaller than unity (0.70). The Pb–Pb bond length in the X-ray



Scheme 3. Synthesis of a plumbylene dimer that is only stable because of LD. The X-ray structure of the product is shown in the vdW surface representation.

structure is 3.06 Å, which is substantially longer than typically observed for Pb–Pb bonds, as found in, for example, hexaphenyldiplumbane (Pb–Pb = 2.84 Å).[155] Thus, the observed dimerization cannot be explained with classical orbital-based donor–acceptor interactions, but rather suggests dispersion-induced dimerization. This conclusion is supported by the fact that the bond energy was computed to be 26.5 kcal mol^{-1} at the M06-2X level, while the dimer was unbound when the B3LYP functional (with moderately sized double-ζ basis sets) was employed. The authors, therefore, conclude (and foresee!) that for many organometallic compounds "*the contributions of attractive dispersion interactions between the experimentally often unavoidable large substituents are neglected although they might be decisive*".[154]

Open and cyclic conformers of *N,N*-dimethylaminopropylsilane (Scheme 4) were exhaustively characterized in the gas phase, in solution, and in the solid state.[156] In the crystalline state, the molecule exists solely in the cyclic form with a weak dative bond, while it displays a dynamic equilibrium in the gas phase with at least three open conformers and a cyclic one. The Si–N bond length (r), for which a bond critical point was located, is 2.91 Å, as determined by gas-phase electron diffraction (GED). Computations at several levels of theory indicate that $r_{\text{Si-N}}$ crucially depends on the treatment of electron correlation and exhibits a scatter from 3.14 Å (HF) to 2.73 Å (MP2). Only high-quality coupled-cluster theory is able to reproduce the experimental bond length satisfactorily. The authors conclude that the weak intramolecular attraction is not only due to electrostatics, but also to dispersion interactions. As a consequence, even small forces are able to distort the geometry significantly because the $r_{\text{Si-N}}$ potential well is very shallow.



Scheme 4. Equilibrium between closed and (several) open forms of *N,N*-dimethylaminopropylsilane. The computed intramolecular Si-N distance (r) is very sensitive to the treatment of electron correlation and only the highest levels of theory are able to reproduce the experimental distance.

LD interactions are also important in media that are dominated by Coulombic forces.[23b] In the protic ionic liquid trihexylammonium triflate, [$(C_6H_{13})_3NH$][CF_3SO_3], ion pairs can in principal show two different modes of interaction: One hydrogen-bonded structure N^+–H···A^- and one in which the anion interacts with the alkyl chains through dispersion, as indicated in the top part of Figure 9. Far-infrared spectra recorded at 303 K show bands at 70 and 130 cm^{-1}, characteristic of a hydrogen-bonded ion pair and correspond to the bond bending and stretching modes of the hydrogen bond. However, when the temperature is increased, these two bands decrease and a new one appears at $\tilde{\nu} = 100$ cm^{-1}. DFT computations helped in the assignment of these spectral features, which apparently are a consequence of the dispersion-assisted interactions on the backside of the N–H bond. A quantitative treatment revealed that the dispersion-bound ion pair is only 8.2 kcal mol^{-1} less stable than the hydrogen-bonded one. This result only emerged when LD was explicitly accounted for in the DFT treatment, and it emphasizes that LD is less temperature-sensitive than dipole-dominated interactions.

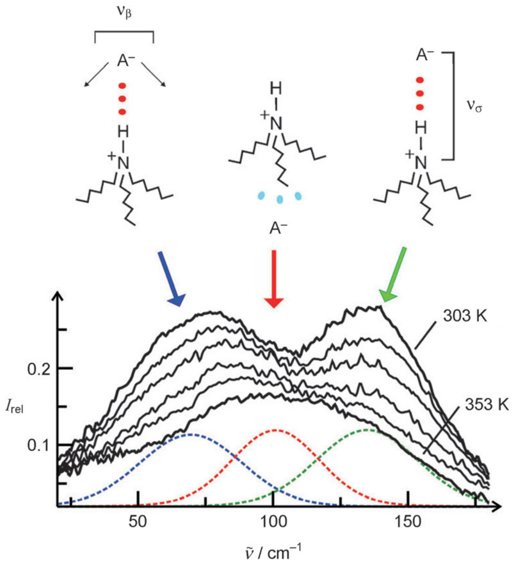


Figure 9. Temperature-dependent far-infrared spectra of the protic ionic liquid [$(C_6H_{13})_3NH$][CF_3SO_3] showing the transition from hydrogen-bonded to dispersion-bound structures upon raising the temperature. Reproduced from Ref. [23b].

Another prominent intermolecular interaction is halogen bonding,[157] which is a subgroup of σ-hole-type interactions.[158] The concept of a σ-hole was introduced to resolve the controversy that electronegative halogen atoms can exhibit attractive noncovalent interactions to Lewis-basic atoms.[159] As a consequence, two formally negatively polarized atoms can interact. This requires that halogen atoms possess regions of positive potential at the opposite ends of their covalent bonds, thus allowing for a favorable overall interaction. LD can be a dominant contributor to this interaction. For prototypical monohalomethane–formaldehyde complexes, SAPT revealed that dispersion makes up 50–60% of the attraction for methyl chloride and bromide.[160] Electrostatics dominate for methyl iodide, as larger halogens allow for larger σ-holes. Fluorine substitution enhances the electrostatic nature of the bond as a result of its polarizing character and small polarizability. Despite the importance of LD, the electrostatic energy component seems to largely determine the geometry of these molecular associates.

2.3. Dispersion Effects on Chemical Reactivity

LD is an important contributor to the reactivity and selectivity of chemical reactions. The explicit inclusion of dispersion effects generally improves the ability of a quantum chemical method to describe chemical reactivity.[42b] It is generally assumed that the introduction of bulky hydrocarbon moieties hampers the reactivity of a chemical system. However, bulky hydrocarbon substituents are also donors of dispersion energy, which means that the interaction with another molecule will be attractive at a particular distance. The idea that London forces accelerate reactions was already put forward in 1964 to explain the relative rates of nucleophilic substitutions of *ortho*-substituted benzyl chlorides.[161] Assuming that LD between a nucleophile and a substituent is important in the *ortho* but not in the *para* position, the authors were able to estimate the contribution of dispersion to the reaction rate experimentally and correlated it to that calculated with London's classic dispersion equation.

Dispersion corrections can lead to new shapes of potential-energy hypersurfaces[162] and often significantly lower the activation barriers, especially for bimolecular reactions.[48b,163] Recently, it has even been stated that "*the TSs of pericyclic reactions may partly be viewed as dispersion-bound*", as the performance of computational methods resembles their ability to deal with noncovalent interactions.[164] For example, it was demonstrated for the Diels–Alder reaction of C_{60} with cyclopentadiene (Figure 10) that a reactant complex could only be located upon addition of a dispersion correction to B3LYP, and the transition-state energy was lowered by 16 kcal mol^{-1}.[48b] Dispersion also influences the stabilities of initial complexes in competing Diels–Alder reactions, thereby affecting rates more than selectivities.[165]

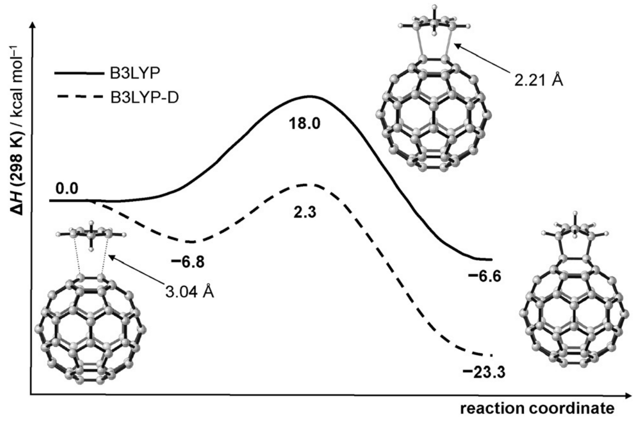
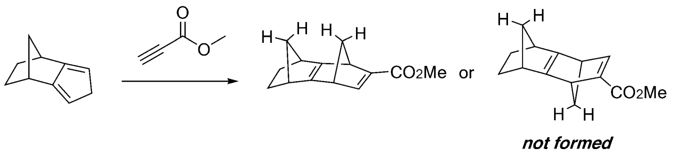


Figure 10. Inclusion of LD (labeled "-D") in the DFT treatment of a Diels–Alder reaction of C_{60} with cyclopentadiene alters the reaction profile. A reactant complex can be located and the transition state is lowered by about 16 kcal mol^{-1}.

Similarly, it was demonstrated in the Diels–Alder reaction of pentacene with C_{60} that the introduction of two bulky 2-trimethylsilylethynyl substituents in the 6- and 13-positions only slightly influences the barrier height.[166] DFT computations even indicate that the transition-state energy is lowered by 1.2 kcal mol^{-1} due to dispersion interactions between the silyl groups and the buckyball. Interestingly, the authors state that this interaction is attractive in the transition state, but it leads to an unfavorable bond stretching in the product and an overall destabilizing steric crowding. This might be rather a general conclusion given that interacting atoms in transition states of additions or fragmentations are farther apart and at distances of the vdW dispersive binding region.

"Steric attraction" also operates in the Diels–Alder reaction between isodicyclopentadiene and methyl propiolate or acrylate (Scheme 5).[167] Here, the formally more crowded *syn* product forms exclusively, which is very uncommon for norbornyl systems. The authors suspected that the steric attraction of the dienophile towards the ethano bridge is greater than to the methano bridge, as a consequence of LD. However, this hypothesis still awaits further validation.



Scheme 5. Diels–Alder reaction of isocyclopentadiene with methyl propiolate to yield the *syn* product exclusively.

If contacts between dispersion energy donors can be attractive in the transition states, it logically follows that it is in principal possible to employ LD to control the selectivity of a chemical reaction. A very similar and meanwhile accepted idea is to direct organic synthesis through hydrophobic interactions[168] by carrying out reactions in water.[169] In such situations, transition states are favored in which the hydrophobic interactions are maximized.[169b] Of course, the major contributor to the hydrophobic effect is entropic, but there is evidence that dispersion should not be underestimated. For example, high selectivity for a 2-naphthyl-substituted olefin was observed in competing epoxidation reactions in water and an only slightly reduced selectivity was observed in a formally nonhydrophobic solvent (isopropyl alcohol/water 1:1), thus indicating that interactions other than hydrophobic ones are also important.[169b,170]

It has long been noticed that aromatic stacking interactions can be employed as control elements in stereoselective organic synthesis.[171] One of the most instructive examples makes use of chiral oxazolidinones in the [4+3] cycloadditions between oxallyl and furan derivatives.[172] Here, the original idea was to shield one of the reactive faces by steric crowding, however, the opposite trend was observed experimentally. DFT computations indicate that only transition structures with both C–O bonds oriented in an antiparallel

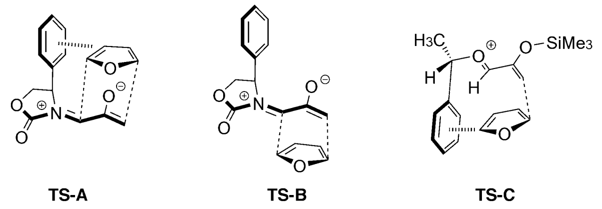


Figure 11. Transition-state geometries of [4+3] cycloadditions, where the formally more crowded ones are favored because of attractive CH-π interactions.

fashion (TS-A and TS-B; Figure 11) are energetically accessible as a result of their dipole moments, even in the presence of $ZnCl_2$ as a Lewis acid. Given this conformation of the oxazolidinone-substituted oxallyl, two modes of attack of the furan are possible, namely to the shielded or the open face of the oxallyl moiety. Dispersion-corrected DFT computations predict that the more crowded TS-A is associated with a 2 kcal mol^{-1} lower barrier than TS-B due to favorable CH-π interactions being absent in TS-B. This is in marked contrast to arguments relating selectivity to steric hindrance.[171]

The same reasoning could be applied to another [4+3] cycloaddition carried out by Hoffmann and co-workers,[173] which was re-examined computationally.[174] Here, furan adds to a chiral alkoxysiloxyallyl cation in a two-step process. The favored transition structure TS-C is essentially dominated by two steric interactions: Firstly, the orientation of the alkoxy substituent minimizes steric repulsion with the hydrogen atom of the allyl cation (comparable to a 1,3-allylic interaction) and, secondly, attractive CH-π contacts determine the preferred face of attack. The selectivity is enhanced when the phenyl substituent is exchanged for a 2-naphthyl group, which provides quantitative diastereoselection; this finding cannot be rationalized on the basis of classic steric (repulsive) arguments.

Reactions which employ LD forces as control elements are in their infancy. Thus far, only a few examples have been reported that utilize attractive π-π and σ-π interactions. However, it should also be possible to utilize attractive σ-σ interactions to stabilize transition structures over those lacking such interactions. In developing this strategy further, it is important to employ rigid DEDs with restricted conformational space, as favorable enthalpic interactions can readily be attenuated by entropic effects. This leaves space for novel reaction design that will advance and challenge our current understanding of chemical reactivity.

2.4. Catalysis: Balancing Steric Repulsion and Dispersion Stabilization in Transition Structures

There is ample evidence that dispersion plays a very important role in catalysis, particularly since small differences in the energy of stereoselective transition structures lead to large changes in chemical selectivity. Many small molecules catalyze reactions with high levels of stereoselectivity, a situation typically associated with large enzymes. As transition states are, in many cases, more polarizable than the reactants because of looser bonds, they are also more sensitive to dispersion effects, a fact that has largely been left unexplored in catalysis.[175] Similarly, as water is only poorly polarizable, any desolvated active site of an enzyme is more polarizable and can thus interact more strongly with the transition state through dispersion,[175] thereby leading to highly effective stabilization of the transition state and hence catalysis.

Although enzymes are viewed as accelerating reactions and imparting selectivity through cooperative stabilization of the transition state, the enantioselectivity imparted by chiral, small-molecule catalysts is rationalized typically by the steric destabilization of all but one dominant pathway. This commonly involved concept has the disadvantage that it is difficult to predetermine the steric demand of functional and ancillary groups in transition states, and this is one of the reasons why rational catalyst design is not straightforward. As it is generally easier to determine stabilizing than repulsive interactions, the quantification of the effects of DEDs on differential transition-state stabilization would be highly valuable. It is currently in its infancy and no general concept has emerged. Considering that the dependence of the Lennard–Jones-type distance on repulsive ($1/R^{12}$) and attractive ($1/R^{6}$) steric interactions is rather different, any loosely bound transition structure must be dominated by the long-range attraction.

Recently, Burns and Jacobsen noted that "*Electrostatic attraction alone is not sufficient to impose the required level of order, because it is direction-independent. This problem could be overcome by incorporating other features into the catalyst, to allow it to orient the charged substrate through attractive, non-covalent interactions …*".[176] This statement originates in a highlight on the success of Čorić and List to carry out enantioselective spiroacetalization using a "spatially confined" Brønsted acid (Figure 12) that is presumed to only leave a small space for the substrate and, therefore, achieves high enantioselectivity.[177]

A closer look at the vdW surface of the catalyst (Figure 12) reveals that an alternative explanation invoking dispersion stabilization of the catalyst and catalyst–substrate structure is not unreasonable given the ideal contact distances of the σ- and π-surfaces. Similarly, size effects and the importance of weak interactions have been well recognized in ligand design for transition-metal-catalyzed reactions.[178] These have been attributed to both steric hindrance and to attractive π-π dispersion forces.[179]

List and co-workers argued in a similar vein in the organocatalytic, enantioselective preparation of azahelicenes in the presence of a 1,1'-spirobiindane-7,7'-diol (SPINOL) derived phosphoric acid derivative with a strong sense of helicity (Figure 13).[180] This beautiful example of a Fischer indolization of appropriately substituted hydrazines and polyaromatic ketones required the long-range control of the stereochemical orientation of both substrates through the catalyst, which was specifically designed to interact through its extended π-faces of the pyrene moieties with the π-faces of the reactants. As the spiro-catalyst itself is helical, it conveys its sense of chirality directly onto the preferred complementarily chiral transition structure (Figure 13). The authors found a clear size–selectivity correlation when replacing the

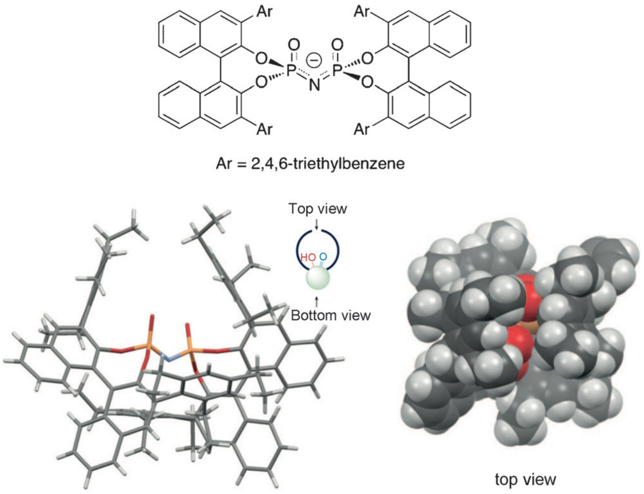


Figure 12. "Spatially confined Brønsted catalyst", which may also be interpreted as being structurally well-defined through stabilizing dispersion interactions that are evident in the van der Waals surface picture on the right.[177] Reprinted from Ref. [177] with permission from Macmillan Publishers Ltd, copyright (2012).

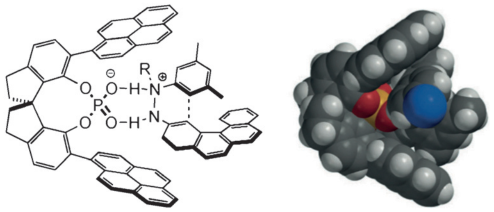


Figure 13. A "spatially compatible Brønsted catalyst" that stabilizes the complementary transition structure through dispersion. A space-filling vdW surface model of the catalyst and the enehydrazine intermediate (right).[180]

pyrene unit with smaller aryl moieties, thereby implying the validity of this concept.

The general problem with the steric argument is that the reactivity of a system would be expected to be very much reduced as the steric encumbrance increases, while the selectivity should increase with increasing steric demand. Oddly, in transition-metal catalysis, reactivity often increases with steric bulk, as expressed in the notion that "*Increased steric bulk on the ligand that buries the metal deep within its fold has been linked to heightened reactivity in cross-coupling procedures.*"[181] This has been shown for a series of increasingly sterically demanding phosphine ligands in Pd-catalyzed cross-coupling reactions (Figure 14).[182] The long list of descriptors and equations to determine steric parameters, such as the Tolman cone angle for phosphine ligands,[183] does not include parameters for dispersion. This may derive from our classic understanding of molecular structures that has been reinforced by the highly successful molecular mechanics approaches that actually have the minimization of "steric strain" as a key optimization parameter, which does not necessarily provide a balanced picture of the effects of sterically demanding substituents and ligand repulsive energies.[184] A view including attractive dispersion interactions through large polarizable catalyst moieties would enable an even more advanced design of catalysts. This requires a much better grasp of the effects of large DEDs in the typical ligand families.

Transition-metal-catalyzed C−X (X = H, Hal, B(OR)$_2$, etc.) bond functionalizations have emerged as attractive alternatives to conventional cross-coupling reactions with sensitive organometallic reagents.[185] Again, the sterically demanding adamantyl substituent in (1-Ad)$_2$P(O)H, which is an air- and moisture-stable preligand for Ru- and Pd-catalyzed direct arylations, gives rise to particularly efficient catalysis (Figure 14).[182b,186] Evidently, dispersion leads to improved self-assembly of the catalysts or catalyst–substrate interactions. This and related catalyst systems (e.g. Beller's adamantyl-substituted CataCXium phosphine ligands)[187] should be probed systematically with a series of ligands for C−X bond functionalization. The improved insight into the ligand interactions will set the stage for more-selective catalysts.

Two striking examples come from computational examinations of dispersion effects in Pd-catalyzed reactions with very bulky metal–phosphine ligand systems, such as [Pd(PPh$_3$)$_4$][188] as well as [Pd(P*t*Bu$_3$)$_2$] and [Pd{P(*i*Pr)*t*Bu$_2$)}$_2$].[162] For the [Pd(PPh$_3$)$_4$] system and its lower coordinated congeners with only one to three phosphine ligands, the inclusion of dispersion in B3LYP computations has a huge effect on the ligand dissociation energies and bring these much closer into agreement with experiment; dispersion corrections to these dissociation energies are as large as 37 kcal mol^{-1}.[188] A change in mechanism was observed when dispersion terms were included in the computations in studies on the competing oxidative addition into the C−Cl versus C−O bond of 4-chlorophenyltriflate (Scheme 6). There were two major findings: Dispersion must be included in the computations to locate very "bulky" transition structures, such as those for oxidative additions with [Pd^0(P*t*Bu$_3$)$_2$], and dispersion interactions control the selectivity in mono- versus bisphosphine-ligated pathways.[162] Remarkably, the dispersion correction to the differential activation free energies ($\Delta\Delta G^{\neq}$) amounts to as much as 30 kcal mol^{-1}, even when including solvation through state-of-the-art techniques.

In the field of stereoselective transition-metal catalysis, interest has grown rapidly regarding the use of noncovalent

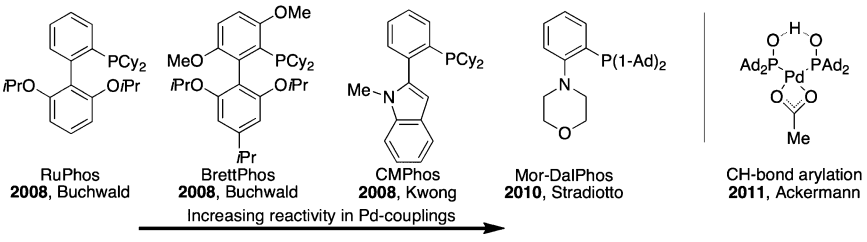
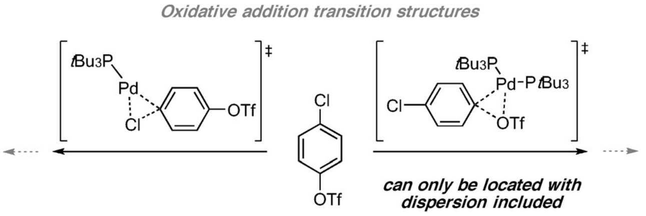


Figure 14. Phosphine ligands in Pd-catalyzed reactions as examples for the counterintuitive notion that increasing bulk provides higher activity and selectivity. Cy = cyclohexyl.



Scheme 6. Model reaction for studying the transition structures for oxidative addition with sterically demanding phosphine ligands with and without the inclusion of dispersion corrections (D) in the DFT approach. Note that the bisligated transition structures could only be located with DFT-D, thus providing a new mechanistic scenario previously not considered.[162]

interactions for the design of pseudobidentate ligands. Monodentate ligands have been developed that are able to self-assemble in the metal coordination sphere through hydrogen bonding or metal-bridged coordinative bonding.[189] To date, the use of dispersion interactions for the rational design of ligands is rather difficult. Although there are many studies dealing with the quantification of hydrogen bonding, π-π stacking, and CH-π (σ-π) interactions as well as their solvent dependence,[190] no conceptual approach has been presented to measure experimentally the contribution of noncovalent ligand–ligand interactions for transition-metal complexes. One such attempt stems from studies on the aggregation of phosphoramidite transition-metal complexes, which is independent of the transition metal, and therefore is determined exclusively by the ligand structure.[191] Another study relates DED size to catalytic activity in palladium-catalyzed Sonogashira reactions, whereby the activity increases when adamantane is replaced with diamantane in their corresponding imidazolium salts, from which carbene ligands are generated in situ by deprotonation.[192]

A particularly striking example comes from the Noyori group, who correlated the enantioselectivity in transfer hydrogenations of aromatic carbonyl compounds with chiral η^6-arene-ruthenium(II) complexes to attractive C-H/π interactions in the diastereoselective transition structures: "… *the enantioselectivity originates not only from the chiral geometry of the five-membered chelate ring but also from the CH/π attractive interaction between the* η^6*-arene ligand and the carbonyl aryl substituent, instead of conventional nonbonded repulsion* …".[193] This observation led to the general notion that aryl substituents in the catalysts are essential for the reduction of aromatic aldehydes and ketones, and the authors encourage a reconsideration of the origin of selectivity and reactivity in other metal-catalyzed reactions.

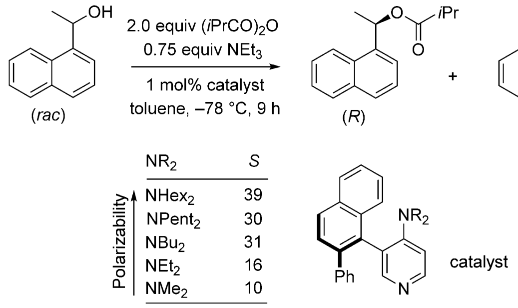
An area of ligand design where dispersion interactions are likely to have a large impact concerns oxidations, such as the catalytic enantioselective epoxidation of unfunctionalized or nonconjugated terminal olefins, which present a formidable challenge because of the absence of polar groups close to the reacting double bond. Hence, all fine-tuning of the catalyst has to rely predominantly on dispersion interactions between the ligand and the substrates. Such reactions have a high potential for large-scale industrial oxidation processes, for which benign approaches are in demand.[194] Currently, the so-called Ti-salalen complexes[195] are the most enantioselective oxidation catalysts. One specific area of research could, therefore, be a reduction in the complexity of the original catalysts to simpler motifs, which have already shown the same performance as, or a better one than, the original catalysts.[196] This concept is supported by the success of disalene ligands with indium as the central metal and $R = R' =$ *tert*-butyl in lactide polymerization.[197]

The importance of intramolecular dispersion interactions for enantioselective organocatalytic reactions has been demonstrated very recently,[198] and it has been shown that, even in short peptides with multiple polar bonds for ionic and hydrogen-bonding interactions, there is still a significant effect derived from dispersion by either shaping the catalyst structure or adding to the substrate recognition.[199] This approach has been important for the use of nonpolar starting materials for organocatalytic reaction sequences[200] that lead to enantiomerically pure products through short peptide multicatalysis as models for small enzymes.[201] The connection between small-molecule and enzymatic catalysis in asymmetric catalysis was made on the basis of attractive noncovalent interactions.[202] Akin to enzymes, noncovalent interactions in general (including hydrogen bonding, dipole–dipole, dispersion, and others) are weaker, less distance-dependent, less directional, and entropy rather than enthalpy controlled.[202,203] Clear parallels exist, for example, in the small-molecule stabilization of oxyanions[202b,204] and hydrophobic amplification of noncovalent organocatalysis in aqueous media.[168]

Organocatalysts are particularly amenable to examining dispersion effects because a highly polarized and polarizing metal center is absent, and all remaining interactions play a larger relative role. Some initial studies in this general direction have already been undertaken, for example, on the asymmetric transfer hydrogenations of ketimines, which react sensitively to formyl-proline amide catalysts with sterically encumbered DEDs in the periphery.[205] It was noted earlier that such reactions and catalysts are operative through both hydrogen bonding and π-π interactions.[206]

Similarly, the inclusion of dispersion interactions in a combined experimental/computational study on the kinetic resolution of secondary alcohols with a systematic series of dimethylaminopyridine (DMAP) derivatives not only improves the agreement between measured and computed barriers, it is essential in recovering the observed kinetic preference for a particular catalyst.[207] This is also immediately evident from the increased S values (with $S = k(R)/k(S)$[208]), which increase for the isobutyrylation with atropisomeric DMAP-derived catalysts as the lipophilicity of the catalyst increases (Scheme 7).

It is tempting to conclude that the combination of the lipophilic anhydride with lipophilic R groups is key to the selectivity, which then essentially goes back to the typical dispersion attractions in simple alkanes. Dispersion and electrostatic interactions can be complementary or competitive, favoring one over the other competing pathways in stereoselective acylation reactions, and this can be successfully used as a design element.[209] This "attractive interaction" in catalyst design, originally formulated for catalyzed Diels–



Scheme 7. Isobutyrylation of a secondary alcohol with an atropisomeric DMAP-derived catalyst with various R groups at the secondary amine: the selectivity *S* in this kinetic resolution increases with the size/polarizability of R.

Alder reactions,[210] was noted in the early 1990s and has also been employed in kinetic resolution with DMAP catalysts with remote stereogenic centers that recognize the substrates dynamically through an induced fit akin to enzyme catalysis.[211]

Even the well-established Houk–List model[212] for understanding the enantioselection in intermolecular aldol reactions catalyzed by proline and some of its derivatives received a fresh interpretation recently, when dispersion interactions were taken into account in the computations.[213] Remarkably, the dispersion corrections to the transition structures amount to 36–39 $\mathrm{kcal\,mol^{-1}}$, a strikingly large number for the assembly of small organic molecules. As a consequence, the agreement between experiment and theory is less good as the sophistication of the theoretical model increases, in particular, with inclusion of dispersion and solvation effects. However, it has since become clear that there are more favorable transition-state conformations[214] than formulated originally and that proline-catalyzed aldol reactions are highly sensitive to the water content of the reaction medium and the reaction temperature, thereby placing stringent conditions on reproducibility. The computational description of intramolecular aldol reactions catalyzed by cinchona alkaloid amines also benefit highly from the inclusion of dispersion, as this substantially improves the agreement between experiment and theory for the stereoselective step; the corrections generally decrease the differences between stereoisomeric transition states for such types of reactions.[215]

Similarly, the selectivity model for the MacMillan imidazolidinone catalyst motifs[216] was first examined without[217] and then with the inclusion of dispersion interactions.[198] A critical study that combined experimental (on the basis of 19 X-ray structures) and high-level computations with and without the inclusion of dispersion effects indicates that the energy difference for the “windshield wiper conformers” (−)-*sc* and (+)-*sc* vary within only ±2 $\mathrm{kcal\,mol^{-1}}$, so that the inclusion of dispersion is crucial. Indeed, the (+)-*sc* conformer for the original MacMillan catalyst with two geminal methyl groups is favored owing to a σ-π interaction between the benzyl group of the catalyst and the *cis*-methyl group of the molecule (Figure 15). This pattern is rather typical and was also found for a large variety of other *cis* substituents.

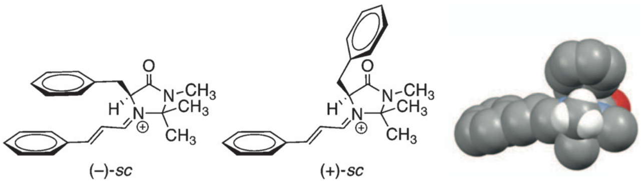


Figure 15. The “windshield-wiper” effect in organocatalysis depends on a fine balance of polar and dispersion interactions: the (+)-*sc* structure with the benzyl group interacting with the methyl group in the 2-position is favored in computations including dispersion effects and in the solid state (space-filling X-ray structure on the right; counterion: $\mathrm{PF_6^-}$).

Decisive dispersion contributions have also surfaced in thiourea catalysis,[218] for which, for example, a change in mechanism by means of reactive substrate–catalyst complexes was uncovered in the Michael addition of oxindoles to nitrostyrene.[219] The experimentally observed stereoselection can only be reproduced theoretically if dispersion is included in the DFT computations. The authors also point out that earlier computations without dispersion may have to be reconsidered.

It is evident that the dispersion stabilization of transition structures has not been looked at in much detail, although it is clear that this is a critical and logical step in improving the rational development of catalysts. The temperature independence of the dispersion interactions also offers practical advantages, as many stereoselective reactions currently require low temperatures. Well-established catalyst platforms including phosphine and carbene ligands, (thio)urea and squareamide derivatives, phosphoric acid (see above), and nucleophilic catalyst families ideally lend themselves to the systematic investigation of DEDs in the design of optimal catalysts, because there is a wealth of information for comparison already available.

2.5. Spectroscopic Signatures of LD

As noted in the Introduction, the consequences of dispersion interactions manifest themselves in a large variety of molecular spectra. At a fundamental level, it is important to remember that the spectral line width of infrared and microwave spectra depend on electrostatic, induction, and dispersion forces. In the last case, the line widths must naturally be related to the mutual spontaneous polarization of the interacting partners.[220] Dispersion is the only force that holds together noble gas clusters (e.g. Ar···Ar with an equilibrium distance of 3.759 Å)[221] and many noble gas/neutral molecule associations; examples include the prototypical benzene–Ar complex, in which the Ar atom is placed centrally above the ring at a distance of 3.58 Å.[222] Such “weakly” (depending on one's point of view) bound complexes have been the playground for the development and refinement of a large variety of spectroscopic techniques. One such technique is zero-electron kinetic energy photoelectron spectroscopy because its spectral resolution is sufficiently high to resolve low-frequency intermolecular modes.[223] The combination of infrared laser photodissociation spectroscopy with time-of-flight mass spectrometry heavily relies on the dispersion interactions of a noble gas atom ("tagging", typically with Ar) to a molecule of interest.[224]

Dispersion interactions between solute and solvent can also significantly affect, for example, forbidden transitions, which may result in additional spectral bands in solution that are absent in the gas phase or in the solid state. A case in point are the so-called infrared "Ham bands"[225] of benzene in a large variety of solvents (e.g. CCl_4, cyclohexane, CH_2Cl_2).[226] This interaction also leads to fluorescence lifetimes that are four to ten times shorter than in uncomplexed benzene.[227]

Stimulated emission pumping resonant two-photon ionization spectroscopy of supersonic jets has been used to probe the dispersion-driven complexes of α-naphthol with benzene and with cyclohexane.[34] Two highly remarkable findings were reported. First, the corresponding interaction energies (D_0) are quite large (5–7 $\mathrm{kcal\,mol^{-1}}$) and—probably surprising to many—the interaction of α-naphthol with cyclohexane is significantly stronger than with benzene! These interactions are also much stronger than, for example, that of a benzene–H_2O complex (2.3 $\mathrm{kcal\,mol^{-1}}$).[228] As the quadrupole moments of these two molecules are quite different and have different signs, these cannot be taken as an explanation for the large differences in the D_0 values based on electrostatics. Although cyclohexane and benzene have about the same perpendicular (to their symmetry axes) polarizabilities, their parallel polarizabilities are quite different: that of cyclohexane is about 50% higher. The authors concluded that the attraction, therefore, must result from intermolecular dispersive and inductive terms,[34] and an excellent linear correlation was found for the parallel molecular polarizabilities of a series of complexes of aromatic molecules with noble gas atoms, benzene, and cyclohexane.

The strength and importance of dispersion interactions can also be gauged by answering conceptually simple but rather fundamental questions. For example, what is the maximum chain length of an unbranched all-*trans* alkane before the chain–chain dispersion interactions would overcome the inevitable synclinal (*gauche*) interactions required to fold the chain into a hairpin-like structure (Figure 16)? This question regarding the most fundamental "organic foldamer" was only answered in 2012 through a combination of sophisticated spectroscopic and computational techniques.[144]

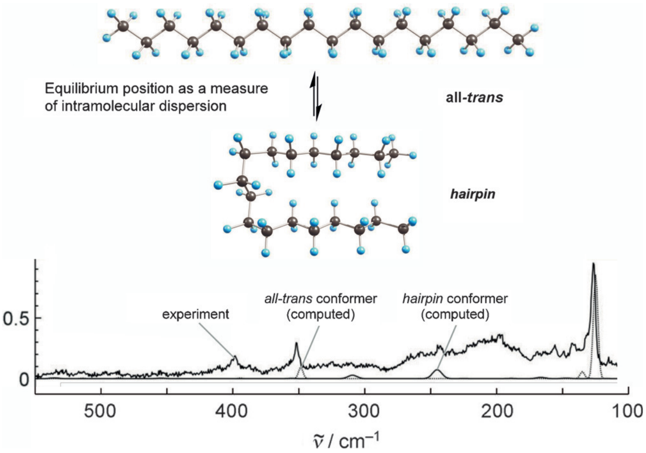
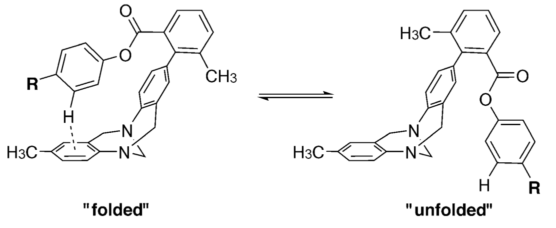


Figure 16. Experimental and simulated low-frequency Raman jet spectra in He expansions of octadecane.[144] Dotted line: all-*trans* spectrum, solid line: double-*gauche* (folded hairpin) structure. Visual inspection of the abundance ratio of the rotamers gives about 15% population of the hairpin structure.

The challenge is to carry out such experiments at very low temperatures, as even *n*-butane is a mixture of conformers at room temperature and any such measurement requires non-equilibrium techniques, as offered, for example, with supersonic jet expansions that allow the generation of molecules with rotational and translational temperatures of about 10 K. Fortunately, the all-*trans* structures have a characteristic Raman "accordion vibration" that correlates with chain length. The authors conclude that unbranched $C_{18}H_{38}$ is probably the "… *last alkane which does not prefer a folded state at low temperature, because it is the last chain which shows a negligible quantity of populated hairpin contributions in* [Figure 16] …".[144] These results provide an upper boundary for the longest unfolded unbranched alkane and it is more likely that the final answer lies with $C_{17}H_{36}$ because it does not profit as much from folding as congeners with an even number of carbon atoms.

Although π-π interactions are commonly invoked to understand binding events in chemistry and even more so in biology, π-π interactions rarely lead to large shifts in the UV/Vis spectra. Hunter and Sanders, therefore, concluded that "*It is a π-σ attraction rather than a π-π electronic interaction which leads to favorable interactions. These electrostatic effects determine the geometry of interaction, while van der Waals interactions (and solvophobic effects) make the major contribution to the magnitude of the observed interaction.*"[110a] The conclusion that a π-σ stabilization is key to aryl–aryl interactions lends weight to the dispersion component of the interaction as well as other factors (e.g. quadrupole interaction). Hunter goes so far in calling this invoking of π-π interactions a misunderstanding under the names of "… *the mythical powers of the "π-π interaction", "π-stacking", "charge transfer" (CT), "π-acid/π-base" or "electron donor acceptor (EDA) interaction* …"[229] The π-σ stabilization picture is also supported by the preferred T-shape of the benzene dimer.[230] Independent support comes from NMR conformational equilibrium measurements on "molecular torsion balances" derived from the Tröger base.[231] The idea is that in a structure with two moderately restricted conformations, one with ("folded") and one without ("unfolded"), a σ-π interaction would act as a sensitive measure of the predominantly entropic restoring force, which depends on intramolecular interactions (Scheme 8). Indeed, such measurements seem to indicate a preference for attractive σ-π interactions in the folded state.[231] When broadly examining other aromatic interactions, Hunter et al. concluded that "*electrostatic forces are not important and that London dispersion forces are more important in governing the edge-to-face interaction.*"[232]

A very similar molecular balance was used to estimate the attenuation of the intramolecular dispersion of medium-



R	folded/unfolded
3,5-Me$_2$	35 : 65
H	60 : 40
p-NO$_2$	75 : 25
p-*t*Bu	80 : 20

Scheme 8. Conformational equilibrium distribution of a selection of aryl esters with π-σ interactions in the folded and unfolded states.

length alkyl chains by solvation.[38a] However, detailed thermodynamic analyses showed that the folded versus unfolded interactions are enthalpy, rather than entropy, driven. In line with this finding, it was demonstrated that increasing the polarizability of the interacting C–H moiety increases the preference for the σ-π interaction. However, the largest contribution seems to originate from local interactions between the *para* substituents and the π-face of the substituted aryl groups.[233]

3. Concluding Remarks and Future Challenges

The notion of van der Waals that "*Matter will always display attraction*"[234] has, at least in part, been forgotten, although we are all aware of the fact that any chemical bonding situation rests on the assumption of a dynamic balance of attractive and repulsive forces. This is the very basis of the atomic hypothesis, as expressed by Feynman in his lectures on physics: "*I believe it is the atomic hypothesis (…) that all things are made of atoms—little particles that move around in perpetual motion, attracting each other when they are a little distance apart, but repelling upon being squeezed into one another.*"[235] This essentially captures what we have tried to do with this Review, namely to demonstrate that there are many cases where LD is surprisingly large and decisively affects molecular structure, reactivity, catalysis, and spectroscopy.

On the practical side, it would be very useful to have available a quantitatively accurate scale of dispersion energy donors (DEDs) that could then be utilized as design elements for chemical synthesis, the construction of new materials, and to fine-tune organic reactivity as well as catalysts. This, however, also requires a reconsideration of "steric and stereoelectronic effects", which are intuitively reasonable but at the same time ignore the quantum nature of electronic interactions.[43] The hard-sphere repulsive model is essentially human because we are so familiar with it on the scale of things we experience in everyday life. However, this is not a good guide for structural models that mostly encompass steric repulsion, thereby ignoring the medium- and long-range electron correlation that essentially results in LD. The human scale aspect was also captured by Feynman in his famous lecture entitled "*There is plenty of room at the bottom*", where he emphasizes that human perception does not translate well to the small scale: "*As we go down in size, there are a number of interesting problems that arise. All things do not simply scale down in proportion. There is the problem that materials stick together by the molecular (van der Waals) attractions. It would be like this: After you have made a part and you unscrew the nut from a bolt, it isn't going to fall down because the gravity isn't appreciable; it would even be hard to get it off the bolt.*"[236]

To date, one of the advantages is that both theory and experimental analytical methods have reached a degree of maturity that allows the examination of chemical structures and their reactivity in unprecedented detail. It was in part the "failure" of the implementation of DFT to not account properly for dispersion that led to the realization that dispersion becomes increasingly important for increasingly larger molecules.[42b] Indeed, most early molecular test sets for gauging the quality of newly developed theoretical models heavily relied on small molecules, for which thermodynamic and spectroscopic data were readily available.[237] At the same time, it is necessary to determine accurate thermochemical and spectroscopic data for larger molecules in the gas phase or in virtually non-interacting media (e.g. helium droplets or noble gas matrices) to probe the increase in the dispersion component to binding and to provide benchmarks for further advancing the development of theoretical methods (e.g. linear scaling algorithms for highly accurate ab initio methods[100]). With accurate data in hand, the attenuation of dispersion in solution and dispersion effects on solutes[226] can also be probed, as the association and desolvation energies are likely to be associated with significant van der Waals interactions.[110a]

Although not covered in this Review, dispersion is also likely to play a very important role in the association of electronically excited molecules, as the occupation of higher-lying orbitals through excitation increases their polarizability. Again, this will require the concomitant development of experimental and theoretical techniques.

One uncomfortable conclusion follows from the descriptions above, namely that structures with long bonds can still be reasonably stable against dissociation. As the bond dissociation energy is determined from the overall interaction energy of the dissociating fragments, it does not necessarily capture the contribution of the broken bond to the total binding. As a consequence, the long-held assumption—initially based on the careful analysis of diatomics—of transferrable bond energies among various structures, can simply not be true for structures that display large intramolecular dispersion contributions. In essence, every bonding situation in every molecule is unique.[33c]

We thank Stefan Grimme and Martin Suhm for fruitful discussions concerning the role and nature of dispersion interactions, and for their collegiality in establishing the Priority Program "Control of Dispersion Interactions in Molecular Chemistry" (SPP 1807) of the Deutsche Forschungs-gemeinschaft, whose support we gratefully acknowl-

edge. J.P.W. thanks the Fonds der Chemischen Industrie for a doctoral fellowship.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 12274–12296
Angew. Chem. **2015**, *127*, 12446–12471

---

[1] K. Autumn, M. Sitti, Y. A. Liang, A. M. Peattie, W. R. Hansen, S. Sponberg, T. W. Kenny, R. Fearing, J. N. Israelachvili, R. J. Full, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 12252.
[2] a) J. D. van der Waals, *Over de Continuiteit van den Gas- en Vloeistoftoestand*, Leiden University (Leiden, The Netherlands), **1873**; b) A. J. Stone, *The Theory of Intermolecular Forces*, Oxford University Press, Oxford, **1997**.
[3] I. G. Kaplan, *Intermolecular Interactions*, Wiley, Chichester, **2006**.
[4] P. Debye, *Polare Molekel*, Leipzig, **1929**.
[5] R. Clausius, *Ann. Phys.* **1857**, *176*, 353.
[6] J. C. Maxwell, *Philos. Trans. R. Soc. London* **1867**, *157*, 49.
[7] L. Boltzmann, *Sitz. Akad. Wiss. Wien* **1872**, *66*, 275.
[8] a) F. London, *Trans. Faraday Soc.* **1937**, *33*, 8b; b) F. London, *Z. Phys.* **1930**, *63*, 245.
[9] R. Eisenschitz, F. London, *Z. Phys.* **1930**, *60*, 491.
[10] K. S. Pitzer, E. Catalano, *J. Am. Chem. Soc.* **1956**, *78*, 4844.
[11] K. S. Pitzer, *J. Chem. Phys.* **1955**, *23*, 1735.
[12] L. S. Bartell, *J. Chem. Phys.* **1960**, *32*, 827.
[13] J. N. Israelachvilli, *Intermolecular and Surface Forces*, 3rd ed., Academic Press, Waltham, USA, **2011**.
[14] F. Biedermann, W. M. Nau, H.-J. Schneider, *Angew. Chem. Int. Ed.* **2014**, *53*, 11158; *Angew. Chem.* **2014**, *126*, 11338.
[15] C. J. van Oss, D. R. Absolom, A. W. Neumann, *Colloid Polym. Sci.* **1980**, *258*, 424.
[16] a) S. Grimme, *Angew. Chem. Int. Ed.* **2006**, *45*, 4460; *Angew. Chem.* **2006**, *118*, 4571; b) P. R. Schreiner, *Angew. Chem. Int. Ed.* **2007**, *46*, 4217; *Angew. Chem.* **2007**, *119*, 4295; c) S. Tsuzuki, H. P. Lüthi, *J. Chem. Phys.* **2001**, *114*, 3949; d) M. J. Allen, D. J. Tozer, *J. Chem. Phys.* **2002**, *117*, 11113; e) S. Kristyán, P. Pulay, *Chem. Phys. Lett.* **1994**, *229*, 175; f) J. M. Pérez-Jordá, A. D. Becke, *Chem. Phys. Lett.* **1995**, *233*, 134.
[17] S. Grimme, C. Mück-Lichtenfeld, J. Antony, *Phys. Chem. Chem. Phys.* **2008**, *10*, 3327.
[18] L. Goerigk, S. Grimme, *Phys. Chem. Chem. Phys.* **2011**, *13*, 6670.
[19] S. Grimme, in *The Chemical Bond* (Eds.: G. Frenking, S. Shaik), Wiley-VCH, Weinheim, **2014**, pp. 477.
[20] a) P. R. Schreiner, L. V. Chernish, P. A. Gunchenko, E. Y. Tikhonchuk, H. Hausmann, M. Serafin, S. Schlecht, J. E. P. Dahl, R. M. K. Carlson, A. A. Fokin, *Nature* **2011**, *477*, 308; b) A. A. Fokin, L. V. Chernish, P. A. Gunchenko, E. Y. Tikhonchuk, H. Hausmann, M. Serafin, J. E. P. Dahl, R. M. K. Carlson, P. R. Schreiner, *J. Am. Chem. Soc.* **2012**, *134*, 13641.
[21] Y. Z. Wang, Y. M. Xie, P. R. Wei, R. B. King, H. F. Schaefer, P. von R. Schleyer, G. H. Robinson, *Science* **2008**, *321*, 1069.
[22] M. J. Cowley, V. Huch, H. S. Rzepa, D. Scheschkewitz, *Nat. Chem.* **2013**, *5*, 876.
[23] a) A. S. Pensado, M. Brehm, J. Thar, A. P. Seitsonen, B. Kirchner, *ChemPhysChem* **2012**, *13*, 1845; b) K. Fumino, V. Fossog, P. Stange, D. Paschek, R. Hempelmann, R. Ludwig, *Angew. Chem. Int. Ed.* **2015**, *54*, 2792; *Angew. Chem.* **2015**, *127*, 2834.
[24] S. Grimme, J.-P. Djukic, *Inorg. Chem.* **2010**, *49*, 2911.
[25] M. Oki, *Acc. Chem. Res.* **1984**, *17*, 154.
[26] a) M. Albrecht, A. Borba, K. Le Barbu-Debus, B. Dittrich, R. Fausto, S. Grimme, A. Mahjoub, M. Nedic, U. Schmitt, L. Schrader, M. A. Suhm, A. Zehnacker-Rentien, J. Zischang, *New J. Chem.* **2010**, *34*, 1266; b) A. Zehnacker, M. A. Suhm, *Angew. Chem. Int. Ed.* **2008**, *47*, 6970; *Angew. Chem.* **2008**, *120*, 7076.
[27] a) P. R. Schreiner, *Angew. Chem. Int. Ed.* **2002**, *41*, 3579; *Angew. Chem.* **2002**, *114*, 3729; b) Y. Mo, J. Gao, *Acc. Chem. Res.* **2007**, *40*, 113.
[28] M. D. Wodrich, C. S. Wannere, Y. Mo, P. D. Jarowski, K. N. Houk, P. von R. Schleyer, *Chem. Eur. J.* **2007**, *13*, 7731.
[29] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.
[30] G. Mayer, S. Pfriem, U. Schäfer, R. Matusch, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 520; *Angew. Chem.* **1978**, *90*, 552.
[31] M. Tanaka, A. Sekiguchi, *Angew. Chem. Int. Ed.* **2005**, *44*, 5821; *Angew. Chem.* **2005**, *117*, 5971.
[32] S. O. Nilsson Lill, P. Ryberg, T. Rein, E. Bennstrom, P. O. Norrby, *Chem. Eur. J.* **2012**, *18*, 1640.
[33] a) G. Frenking, S. Shaik, *The Chemical Bond. Fundamental Aspects of Chemical Bonding*, Wiley-VCH, Weinheim, **2014**; b) G. Frenking, S. Shaik, *The Chemical Bond. Chemical Bonding Across the Periodic Table*, Wiley-VCH, Weinheim, **2014**; c) P. Ball, *Chem. World* **2014**, 50.
[34] C. Wickleder, T. Droz, T. Burgi, S. Leutwyler, *Chem. Phys. Lett.* **1997**, *264*, 257.
[35] I. E. Craven, M. R. Hesling, D. R. Laver, P. B. Lukins, G. L. D. Ritchie, J. Vrbancich, *J. Phys. Chem.* **1989**, *93*, 627.
[36] A. Fujii, H. Hayashi, J. W. Park, T. Kazama, N. Mikami, S. Tsuzuki, *Phys. Chem. Chem. Phys.* **2011**, *13*, 14131.
[37] R. H. French, *J. Am. Ceram. Soc.* **2000**, *83*, 2117.
[38] a) L. Yang, C. Adam, G. S. Nichol, S. L. Cockroft, *Nat. Chem.* **2013**, *5*, 1006; b) A. D. McLachlan, *Discuss. Faraday Soc.* **1965**, *40*, 239.
[39] S. Hanlon, *Biochem. Biophys. Res. Commun.* **1966**, *23*, 861.
[40] J. Poater, M. Swart, C. F. Guerra, F. M. Bickelhaupt, *Chem. Commun.* **2011**, *47*, 7326.
[41] H. Aikawa, Y. Takahira, M. Yamaguchi, *Chem. Commun.* **2011**, *47*, 1479.
[42] a) K. E. Riley, P. Hobza, *WIREs Comput. Mol. Sci.* **2011**, *1*, 3; b) S. Grimme, *WIREs Comput. Mol. Sci.* **2011**, *1*, 211; c) C. Corminboeuf, *Acc. Chem. Res.* **2014**, *47*, 3217; d) E. G. Hohenstein, C. D. Sherrill, *WIREs Comput. Mol. Sci.* **2012**, *2*, 304.
[43] O. Takahashi, Y. Kohno, M. Nishio, *Chem. Rev.* **2010**, *110*, 6049.
[44] H. Margenau, *J. Chem. Phys.* **1938**, *6*, 896.
[45] K. F. Herzfeld, *Phys. Rev.* **1927**, *29*, 701.
[46] a) K. Szalewicz, *WIREs Comput. Mol. Sci.* **2012**, *2*, 254; b) G. Jansen, *WIREs Comput. Mol. Sci.* **2014**, *4*, 127.
[47] S. Grimme, J. Antony, T. Schwabe, C. Muck-Lichtenfeld, *Org. Biomol. Chem.* **2007**, *5*, 741.
[48] a) S. Grimme, R. Huenerbein, S. Ehrlich, *ChemPhysChem* **2011**, *12*, 1258; b) S. L. Osuna, M. Swart, M. Solà, *J. Phys. Chem. A* **2011**, *115*, 3491.
[49] K. Kitaura, K. Morokuma, *Int. J. Quantum Chem.* **1976**, *10*, 325.
[50] S. N. Steinmann, C. Corminboeuf, *J. Chem. Theory Comput.* **2011**, *7*, 3567.
[51] E. R. Davidson, D. Feller, *Chem. Rev.* **1986**, *86*, 681.
[52] S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553.
[53] J. T. H. Dunning, *J. Chem. Phys.* **1989**, *90*, 1007.
[54] R. A. Kendall, T. H. Dunning, R. J. Harrison, *J. Chem. Phys.* **1992**, *96*, 6796.
[55] R. J. Bartlett, C. E. Dykstra, J. Paldus, in *Advanced Theories and Computational Approaches to the Electronic Structure of Molecules* (Ed.: C. E. Dykstra), Reidel, Dordrecht, **1984**, pp. 127.
[56] T. D. Crawford, H. F. Schaefer, in *Rev. Comput. Chem.*, Wiley, New York, **2007**, pp. 33.
[57] A. G. Császár, W. D. Allen, H. F. Schaefer, *J. Chem. Phys.* **1998**, *108*, 9751.
[58] A. Halkier, T. Helgaker, P. Jørgensen, W. Klopper, H. Koch, J. Olsen, A. K. Wilson, *Chem. Phys. Lett.* **1998**, *286*, 243.
[59] M. W. Feyereisen, G. Fitzgerald, A. Komornicki, *Chem. Phys. Lett.* **1993**, *208*, 359.

[60] a) C. D. Sherrill, T. Takatani, E. G. Hohenstein, *J. Phys. Chem. A* **2009**, *113*, 10146; b) S. Tsuzuki, K. Honda, T. Uchimaru, M. Mikami, *J. Chem. Phys.* **2006**, *124*, 114304; c) J. P. Wagner, P. R. Schreiner, *J. Chem. Theory Comput.* **2014**, *10*, 1353.
[61] M. O. Sinnokrot, C. D. Sherrill, *J. Phys. Chem. A* **2006**, *110*, 10656.
[62] S. Grimme, *J. Chem. Phys.* **2003**, *118*, 9095.
[63] J. Antony, S. Grimme, *J. Phys. Chem. A* **2007**, *111*, 4862.
[64] S. Grimme, L. Goerigk, R. F. Fink, *WIREs Comput. Mol. Sci.* **2012**, *2*, 886.
[65] T. Takatani, E. G. Hohenstein, C. D. Sherrill, *J. Chem. Phys.* **2008**, *128*, 124111.
[66] S. Ten-no, J. Noga, *WIREs Comput. Mol. Sci.* **2012**, *2*, 114.
[67] a) F. Neese, A. Hansen, F. Wennmohs, S. Grimme, *Acc. Chem. Res.* **2009**, *42*, 641; b) F. Neese, A. Hansen, D. G. Liakos, *J. Chem. Phys.* **2009**, *131*, 064103.
[68] a) J. Pérez-Jordá, A. D. Becke, *Chem. Phys. Lett.* **1995**, *233*, 134; b) P. Hobza, J. Sponer, T. Reschel, *J. Comput. Chem.* **1995**, *16*, 1315.
[69] H. Kruse, L. Goerigk, S. Grimme, *J. Org. Chem.* **2012**, *77*, 10824.
[70] J. Klimeš, A. Michaelides, *J. Chem. Phys.* **2012**, *137*, 120901.
[71] J. P. Perdew, K. Schmidt, *AIP Conf. Proc.* **2001**, *577*, 1.
[72] a) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215; b) Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157.
[73] Y. Zhao, D. G. Truhlar, *J. Chem. Phys.* **2006**, *125*, 194101.
[74] E. G. Hohenstein, S. T. Chill, C. D. Sherrill, *J. Chem. Theory Comput.* **2008**, *4*, 1996.
[75] a) J. Hepburn, G. Scoles, R. Penco, *Chem. Phys. Lett.* **1975**, *36*, 451; b) R. Ahlrichs, R. Penco, G. Scoles, *Chem. Phys.* **1977**, *19*, 119.
[76] a) M. Elstner, P. Hobza, T. Frauenheim, S. Suhai, E. Kaxiras, *J. Chem. Phys.* **2001**, *114*, 5149; b) Q. Wu, W. Yang, *J. Chem. Phys.* **2002**, *116*, 515.
[77] S. Grimme, *J. Comput. Chem.* **2004**, *25*, 1463.
[78] S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787.
[79] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456.
[80] a) A. Tkatchenko, A. Ambrosetti, R. A. DiStasio, Jr., *J. Chem. Phys.* **2013**, *138*, 074106; b) Y. Li, D. Lu, H.-V. Nguyen, G. Galli, *J. Phys. Chem. A* **2010**, *114*, 1944.
[81] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.
[82] S. Grimme, *Angew. Chem. Int. Ed.* **2008**, *47*, 3430; *Angew. Chem.* **2008**, *120*, 3478.
[83] A. Tkatchenko, M. Scheffler, *Phys. Rev. Lett.* **2009**, *102*, 073005.
[84] A. D. Becke, E. R. Johnson, *J. Chem. Phys.* **2005**, *122*, 154104.
[85] M. Dion, H. Rydberg, E. Schröder, D. C. Langreth, B. I. Lundqvist, *Phys. Rev. Lett.* **2004**, *92*, 246401.
[86] O. A. Vydrov, T. Van Voorhis, *Phys. Rev. Lett.* **2009**, *103*, 063004.
[87] O. A. Vydrov, T. Van Voorhis, *J. Chem. Phys.* **2010**, *133*, 244103.
[88] W. Hujo, S. Grimme, *J. Chem. Theory Comput.* **2013**, *9*, 308.
[89] L. Goerigk, S. Grimme, *WIREs Comput. Mol. Sci.* **2014**, *4*, 576.
[90] S. Grimme, *J. Chem. Phys.* **2006**, *124*, 034108/1.
[91] A. D. Becke, *J. Chem. Phys.* **2014**, *140*, 18A301.
[92] E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 6498.
[93] R. F. W. Bader, in *Atoms in Molecules*, in *Encyclopedia of Computational Chemistry* (Eds: P. von R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, P. R. Schreiner), Wiley, New York, **2002**.
[94] J. R. Lane, J. Contreras-García, J.-P. Piquemal, B. J. Miller, H. G. Kjaergaard, *J. Chem. Theory Comput.* **2013**, *9*, 3263.
[95] J. Contreras-García, E. R. Johnson, S. Keinan, R. Chaudret, J.-P. Piquemal, D. N. Beratan, W. Yang, *J. Chem. Theory Comput.* **2011**, *7*, 625.
[96] M. Alonso, T. Woller, F. J. Martin-Martinez, J. Contreras-García, P. Geerlings, F. De Proft, *Chem. Eur. J.* **2014**, *20*, 4931.
[97] D. Danovich, S. Shaik, F. Neese, J. Echeverría, G. Aullón, S. Alvarez, *J. Chem. Theory Comput.* **2013**, *9*, 1977.
[98] J. Echeverría, G. Aullon, D. Danovich, S. Shaik, S. Alvarez, *Nat. Chem.* **2011**, *3*, 323.
[99] Y. Mo, P. Bao, J. Gao, *Phys. Chem. Chem. Phys.* **2011**, *13*, 6760.
[100] S. A. Maurer, M. Beer, D. S. Lambrecht, C. Ochsenfeld, *J. Chem. Phys.* **2013**, *139*, 184104.
[101] A. K. Rappé, E. R. Bernstein, *J. Phys. Chem. A* **2000**, *104*, 6117.
[102] B. P. Reid, M. J. O'Loughlin, R. K. Sparks, *J. Chem. Phys.* **1985**, *83*, 5656.
[103] Y. Cho, W. J. Cho, I. S. Youn, G. Lee, N. J. Singh, K. S. Kim, *Acc. Chem. Res.* **2014**, *47*, 3321.
[104] S. Tsuzuki, K. Honda, T. Uchimaru, M. Mikami, *J. Phys. Chem. A* **2004**, *108*, 10311.
[105] A. Salam, M. S. Deleuze, *J. Chem. Phys.* **2002**, *116*, 1296.
[106] A. A. Fokin, D. Gerbig, P. R. Schreiner, *J. Am. Chem. Soc.* **2011**, *133*, 20036.
[107] T. Janowski, P. Pulay, *J. Am. Chem. Soc.* **2012**, *134*, 17520.
[108] C. Wang, Y. Mo, J. P. Wagner, P. R. Schreiner, E. D. Jemmis, D. Danovich, S. Shaik, *J. Chem. Theory Comput.* **2015**, *11*, 1621.
[109] a) J. S. Sinninghe Damsté, M. Strous, W. I. C. Rijpstra, E. C. Hopmans, J. A. J. Geenevasen, A. C. T. van Duin, L. A. van Niftrik, M. S. M. Jetten, *Nature* **2002**, *419*, 708; b) H. Hopf, *Angew. Chem. Int. Ed.* **2003**, *42*, 2822; *Angew. Chem.* **2003**, *115*, 2928.
[110] a) C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525; b) K. Müller-Dethlefs, P. Hobza, *Chem. Rev.* **1999**, *100*, 143; c) K. S. Kim, P. Tarakeshwar, J. Y. Lee, *Chem. Rev.* **2000**, *100*, 4145.
[111] C. R. Martinez, B. L. Iverson, *Chem. Sci.* **2012**, *3*, 2191.
[112] a) M. Nishio, *Phys. Chem. Chem. Phys.* **2011**, *13*, 13873; b) M. Nishio, M. Hirota, Y. Umezawa, *The CH/π Interaction. Evidence, Nature and Consequences*, Wiley-VCH, Weinheim, **1998**.
[113] Y. Morino, K. Kuchitsu, *J. Chem. Phys.* **1958**, *28*, 175.
[114] E. Hirota, *J. Chem. Phys.* **1962**, *37*, 283.
[115] a) P. R. Schreiner, A. A. Fokin, R. A. Pascal, A. de Meijere, *Org. Lett.* **2006**, *8*, 3635; b) M. D. Wodrich, C. Corminboeuf, P. R. Schreiner, A. A. Fokin, P. von R. Schleyer, *Org. Lett.* **2007**, *9*, 1851.
[116] Y. Zhao, D. G. Truhlar, *Org. Lett.* **2006**, *8*, 5753.
[117] M. D. Wodrich, C. Corminboeuf, P. von R. Schleyer, *Org. Lett.* **2006**, *8*, 3631.
[118] S. Gronert, *Chem. Eur. J.* **2009**, *15*, 5372.
[119] T. L. Allen, *J. Chem. Phys.* **1958**, *29*, 951.
[120] W. C. McKee, P. von R. Schleyer, *J. Am. Chem. Soc.* **2013**, *135*, 13008.
[121] S. Grimme, *Org. Lett.* **2010**, *12*, 4670.
[122] R. E. Carter, B. Nilsson, K. Olsson, *J. Am. Chem. Soc.* **1975**, *97*, 6155.
[123] M. H. Lyttle, A. Streitwieser, R. Q. Kluttz, *J. Am. Chem. Soc.* **1981**, *103*, 3232.
[124] L. A. Paquette, G. J. Hefferon, R. Samodral, Y. Hanzawa, *J. Org. Chem.* **1983**, *48*, 1262.
[125] N. L. Allinger, M. Frierson, F. A. Van-Catledge, *J. Am. Chem. Soc.* **1982**, *104*, 4592.
[126] J. S. Ghotra, M. B. Hursthouse, A. J. Welch, *J. Chem. Soc. Chem. Commun.* **1973**, 669.
[127] J. M. McBride, *Tetrahedron* **1974**, *30*, 2009.
[128] W. D. Hounshell, D. A. Dougherty, J. P. Hummel, K. Mislow, *J. Am. Chem. Soc.* **1977**, *99*, 1916.
[129] B. Kahr, D. van Engen, K. Mislow, *J. Am. Chem. Soc.* **1986**, *108*, 8305.

[130] a) E. Osawa, Y. Onuki, K. Mislow, *J. Am. Chem. Soc.* **1981**, *103*, 7475; b) G. A. Olah, L. D. Field, M. Watkins, R. Malhotra, *J. Org. Chem.* **1981**, *46*, 1761.

[131] T. Vreven, K. Morokuma, *J. Phys. Chem. A* **2002**, *106*, 6167.

[132] a) M. Gomberg, *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3150; b) M. Gomberg, *J. Am. Chem. Soc.* **1900**, *22*, 757.

[133] H. Lankamp, W. T. Nauta, C. Maclean, *Tetrahedron Lett.* **1968**, *9*, 249.

[134] P. W. Selwood, R. M. Dobres, *J. Am. Chem. Soc.* **1950**, *72*, 3860.

[135] S. Grimme, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2011**, *50*, 12639; *Angew. Chem.* **2011**, *123*, 12849.

[136] K. Goto, T. Kubo, K. Yamamoto, K. Nakasuji, K. Sato, D. Shiomi, T. Takui, M. Kubota, T. Kobayashi, K. Yakusi, J. Y. Ouyang, *J. Am. Chem. Soc.* **1999**, *121*, 1619.

[137] a) Z.-h. Cui, H. Lischka, H. Z. Beneberu, M. Kertesz, *J. Am. Chem. Soc.* **2014**, *136*, 5539; b) B. Kolb, M. Kertesz, T. Thonhauser, *J. Phys. Chem. A* **2013**, *117*, 3642.

[138] S. Suzuki, Y. Morita, K. Fukui, K. Sato, D. Shiomi, T. Takui, K. Nakasuji, *J. Am. Chem. Soc.* **2006**, *128*, 2530.

[139] Z. Mou, K. Uchida, T. Kubo, M. Kertesz, *J. Am. Chem. Soc.* **2014**, *136*, 18009.

[140] F. Mota, J. S. Miller, J. J. Novoa, *J. Am. Chem. Soc.* **2009**, *131*, 7699.

[141] R. Mondal, C. Tonshoff, D. Khon, D. C. Neckers, H. F. Bettinger, *J. Am. Chem. Soc.* **2009**, *131*, 14281.

[142] a) H. F. Bettinger, R. Mondal, D. C. Neckers, *Chem. Commun.* **2007**, 5209; b) C. Tönshoff, H. F. Bettinger, *Angew. Chem. Int. Ed.* **2010**, *49*, 4125; *Angew. Chem.* **2010**, *122*, 4219.

[143] S. Ehrlich, H. F. Bettinger, S. Grimme, *Angew. Chem. Int. Ed.* **2013**, *52*, 10892; *Angew. Chem.* **2013**, *125*, 11092.

[144] N. O. B. Lüttschwager, T. N. Wassermann, R. A. Mata, M. A. Suhm, *Angew. Chem. Int. Ed.* **2013**, *52*, 463; *Angew. Chem.* **2013**, *125*, 482.

[145] a) H. Schwertfeger, A. A. Fokin, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008**, *47*, 1022; *Angew. Chem.* **2008**, *120*, 1038; b) M. A. Gunawan, J.-C. Hierso, D. Poinsot, A. A. Fokin, N. A. Fokina, B. A. Tkachenko, P. R. Schreiner, *New J. Chem.* **2014**, *38*, 28.

[146] K. M. N. de Silva, J. M. Goodman, *J. Chem. Inf. Model.* **2005**, *45*, 81.

[147] M. Kaupp, B. Metz, H. Stoll, *Angew. Chem. Int. Ed.* **2000**, *39*, 4607; *Angew. Chem.* **2000**, *112*, 4780.

[148] A. A. Zavitsas, *J. Phys. Chem. A* **2003**, *107*, 897.

[149] a) W. Gordy, *J. Chem. Phys.* **1946**, *14*, 305; b) M. L. Huggins, *J. Am. Chem. Soc.* **1953**, *75*, 4126.

[150] L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, New York, **1960**.

[151] G. Fritz, S. Wartanessian, E. Matern, W. Hönle, H. G. von Schnering, *Z. Anorg. Allg. Chem.* **1981**, *475*, 87.

[152] a) R. Winiker, H. D. Beckhaus, C. Rüchardt, *Chem. Ber.-Recl.* **1980**, *113*, 3456; b) M. A. Flamm-ter Meer, H. D. Beckhaus, K. Peters, H. G. von Schnering, C. Rüchardt, *Chem. Ber.-Recl.* **1985**, *118*, 4665.

[153] C. Rüchardt, H.-D. Beckhaus, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 529; *Angew. Chem.* **1985**, *97*, 531.

[154] H. Arp, J. Baumgartner, C. Marschner, P. Zark, T. Müller, *J. Am. Chem. Soc.* **2012**, *134*, 6409.

[155] V. H. Preut, H.-J. Haupt, F. Huber, *Z. Anorg. Allg. Chem.* **1973**, *396*, 81.

[156] M. Hagemann, R. J. F. Berger, S. A. Hayes, H.-G. Stammler, N. W. Mitzel, *Chem. Eur. J.* **2008**, *14*, 11027.

[157] S. H. Jungbauer, S. M. Walter, S. Schindler, L. Rout, F. Kniep, S. M. Huber, *Chem. Commun.* **2014**, *50*, 6281.

[158] T. Clark, M. Hennemann, J. S. Murray, P. Politzer, *J. Mol. Model.* **2006**, *13*, 291.

[159] T. Clark, *WIREs Comput. Mol. Sci.* **2013**, *3*, 13.

[160] K. E. Riley, P. Hobza, *J. Chem. Theory Comput.* **2008**, *4*, 232.

[161] D. L. Dalrymple, J. D. Reinheimer, D. Barnes, R. Baker, *J. Org. Chem.* **1964**, *29*, 2647.

[162] E. Lyngvi, I. A. Sanhueza, F. Schoenebeck, *Organometallics* **2015**, *34*, 805.

[163] R. Lonsdale, J. N. Harvey, A. J. Mulholland, *J. Chem. Theory Comput.* **2012**, *8*, 4637.

[164] A. Karton, L. Goerigk, *J. Comput. Chem.* **2015**, *36*, 622.

[165] I. Fernández, M. Solà, F. M. Bickelhaupt, *Chem. Eur. J.* **2013**, *19*, 7416.

[166] Y. Cao, Y. Liang, L. Zhang, S. Osuna, A.-L. M. Hoyt, A. L. Briseno, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 10743.

[167] T. Sugimoto, Y. Kobuke, J. Furukawa, *J. Org. Chem.* **1976**, *41*, 1457.

[168] C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315.

[169] a) M. Raj, V. K. Singh, *Chem. Commun.* **2009**, 6687; b) U. M. Lindström, F. Andersson, *Angew. Chem. Int. Ed.* **2006**, *45*, 548; *Angew. Chem.* **2006**, *118*, 562; c) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.* **2006**, *45*, 958; *Angew. Chem.* **2006**, *118*, 972; d) A. Wittkopp, P. R. Schreiner, in *The Chemistry of Dienes and Polyenes.*, *Vol. 2* (Ed.: Z. Rappoport), Wiley, Chichester, **2000**, pp. 1029; e) J. B. F. N. Engberts, *Pure Appl. Chem.* **1995**, *67*, 823; f) W. Blokzijl, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **1992**, *114*, 5440; g) R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159; h) P. A. Grieco, S. D. Larsen, W. F. Fobare, *Tetrahedron Lett.* **1986**, *27*, 1975.

[170] M. R. Biscoe, R. Breslow, *J. Am. Chem. Soc.* **2005**, *127*, 10812.

[171] E. H. Krenske, K. N. Houk, *Acc. Chem. Res.* **2013**, *46*, 979.

[172] E. H. Krenske, K. N. Houk, M. Harmata, *Org. Lett.* **2010**, *12*, 444.

[173] C. B. W. Stark, U. Eggert, H. M. R. Hoffmann, *Angew. Chem. Int. Ed.* **1998**, *37*, 1266; *Angew. Chem.* **1998**, *110*, 1337.

[174] E. H. Krenske, K. N. Houk, A. G. Lohse, J. E. Antoline, R. P. Hsung, *Chem. Sci.* **2010**, *1*, 387.

[175] S. M. Ngola, D. A. Dougherty, *J. Org. Chem.* **1996**, *61*, 4355.

[176] N. Z. Burns, E. N. Jacobsen, *Nature* **2012**, *483*, 278.

[177] I. Čorić, B. List, *Nature* **2012**, *483*, 315.

[178] R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.

[179] C. Lima, M. A. A. Rocha, L. R. Gomes, J. N. Low, A. M. S. Silva, L. Santos, *Chem. Eur. J.* **2012**, *18*, 8934.

[180] L. Kötzner, M. J. Webber, A. Martínez, C. De Fusco, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 5202; *Angew. Chem.* **2014**, *126*, 5303.

[181] C. Valente, S. Calimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314; *Angew. Chem.* **2012**, *124*, 3370.

[182] a) B. P. Fors, P. Krattiger, E. Strieter, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 3505; b) L. Ackermann, S. Barfusser, C. Kornhaass, A. R. Kapdi, *Org. Lett.* **2011**, *13*, 3082.

[183] a) C. A. Tolman, *J. Am. Chem. Soc.* **1970**, *92*, 2956; b) J. A. Bilbrey, A. H. Kazez, J. Locklin, W. D. Allen, *J. Comput. Chem.* **2013**, *34*, 1189.

[184] D. P. White, J. C. Anthony, A. O. Oyefeso, *J. Org. Chem.* **1999**, *64*, 7707.

[185] L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.

[186] L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619; *Angew. Chem.* **2006**, *118*, 2681.

[187] a) A. G. Sergeev, A. Zapf, A. Spannenberg, M. Beller, *Organometallics* **2008**, *27*, 297; b) H. Neumann, A. Brennführer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645; c) T. Schareina, A. Zapf, W. Magerlein, N. Muller, M. Beller, *Tetrahedron Lett.* **2007**, *48*, 1087.

[188] M. S. Ahlquist, P. O. Norrby, *Angew. Chem. Int. Ed.* **2011**, *50*, 11794; *Angew. Chem.* **2011**, *123*, 11998.

[189] B. Breit, *Angew. Chem. Int. Ed.* **2005**, *44*, 6816; *Angew. Chem.* **2005**, *117*, 6976.

[190] a) S. L. Cockroft, C. A. Hunter, *Chem. Soc. Rev.* **2007**, *36*, 172; b) S. L. Cockroft, C. A. Hunter, *Chem. Commun.* **2006**, 3806.
[191] a) K. Schober, E. Hartmann, H. X. Zhang, R. M. Gschwind, *Angew. Chem. Int. Ed.* **2010**, *49*, 2794; *Angew. Chem.* **2010**, *122*, 2855; b) K. Schober, H. X. Zhang, R. M. Gschwind, *J. Am. Chem. Soc.* **2008**, *130*, 12310.
[192] H. Richter, H. Schwertfeger, P. R. Schreiner, R. Fröhlich, F. Glorius, *Synlett* **2009**, 193.
[193] M. Yamakawa, I. Yamada, R. Noyori, *Angew. Chem. Int. Ed.* **2001**, *40*, 2818; *Angew. Chem.* **2001**, *113*, 2900.
[194] a) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5; b) J. Crosby, *Tetrahedron* **1991**, *47*, 4789.
[195] a) Y. Sawada, K. Matsumoto, S. Kondo, H. Watanabe, T. Ozawa, K. Suzuki, B. Saito, T. Katsuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3478; *Angew. Chem.* **2006**, *118*, 3558; b) K. Matsumoto, Y. Sawada, B. Saito, K. Sakai, T. Katsuki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4935; *Angew. Chem.* **2005**, *117*, 5015.
[196] a) A. Berkessel, M. Brandenburg, E. Leitterstorf, J. Frey, J. Lex, M. Schafer, *Adv. Synth. Catal.* **2007**, *349*, 2385; b) A. Berkessel, M. Brandenburg, *Org. Lett.* **2006**, *8*, 4401.
[197] D. C. Aluthge, B. O. Patrick, P. Mehrkhodavandi, *Chem. Commun.* **2013**, *49*, 4295.
[198] D. Seebach, U. Grošelj, W. B. Schweizer, S. Grimme, C. Mück-Lichtenfeld, *Helv. Chim. Acta* **2010**, *93*, 1.
[199] C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008**, *47*, 6180; *Angew. Chem.* **2008**, *120*, 6275.
[200] R. Hrdina, C. E. Müller, R. C. Wende, L. Wanka, P. R. Schreiner, *Chem. Commun.* **2012**, *48*, 2498.
[201] R. C. Wende, P. R. Schreiner, *Green Chem.* **2012**, *14*, 1821.
[202] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) Z. G. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187.
[203] R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678.
[204] M. Kotke, P. R. Schreiner, *Synthesis* **2007**, 779.
[205] Z. G. Zhang, P. Rooshenas, H. Hausmann, P. R. Schreiner, *Synthesis* **2009**, 1531.
[206] A. V. Malkov, A. Mariani, K. N. MacDougall, P. Kočovský, *Org. Lett.* **2004**, *6*, 2253.
[207] E. Larionov, M. Mahesh, A. C. Spivey, Y. Wei, H. Zipse, *J. Am. Chem. Soc.* **2012**, *134*, 9390.
[208] H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249.
[209] Y. Wei, I. Held, H. Zipse, *Org. Biomol. Chem.* **2006**, *4*, 4223.
[210] a) J. M. Hawkins, S. Loren, *J. Am. Chem. Soc.* **1991**, *113*, 7794; b) E. J. Corey, T. P. Loh, *J. Am. Chem. Soc.* **1991**, *113*, 8966.
[211] T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169.
[212] S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475.
[213] A. Armstrong, R. A. Boto, P. Dingwall, J. Contreras-García, M. J. Harvey, N. J. Mason, H. S. Rzepa, *Chem. Sci.* **2014**, *5*, 2057.
[214] P. H. Y. Cheong, C. Y. Legault, J. M. Um, N. Celebi-Olcum, K. N. Houk, *Chem. Rev.* **2011**, *111*, 5042.
[215] Y. H. Lam, K. N. Houk, *J. Am. Chem. Soc.* **2015**, *137*, 2116.
[216] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.
[217] R. Gordillo, J. Carter, K. N. Houk, *Adv. Synth. Catal.* **2004**, *346*, 1175.
[218] a) K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919; b) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986.
[219] C. Reiter, S. Lopez-Molina, B. Schmid, C. Neiss, A. Goerling, S. B. Tsogoeva, *ChemCatChem* **2014**, *6*, 1324.
[220] Krishnaji, S. L. Srivastava, *J. Chem. Phys.* **1964**, *41*, 2266.
[221] E. A. Colbourn, A. E. Douglas, *J. Chem. Phys.* **1976**, *65*, 1741.
[222] T. Weber, E. Riedle, H. J. Neusser, E. W. Schlag, *Chem. Phys. Lett.* **1991**, *183*, 77.
[223] a) C. E. H. Dessent, K. Müller-Dethlefs, *Chem. Rev.* **2000**, *100*, 3999; b) K. Müller-Dethlefs, O. Dopfer, T. G. Wright, *Chem. Rev.* **1994**, *94*, 1845.
[224] a) M. Okumura, L. I. Yeh, J. D. Myers, Y. T. Lee, *J. Chem. Phys.* **1986**, *85*, 2328; b) D. W. Boo, Z. F. Liu, A. G. Suits, J. S. Tse, Y. T. Lee, *Science* **1995**, *269*, 57; c) M. A. Duncan, *J. Phys. Chem. A* **2012**, *116*, 11477.
[225] J. S. Ham, *J. Chem. Phys.* **1953**, *21*, 756.
[226] M. Koyanagi, *J. Mol. Spectrosc.* **1968**, *25*, 273.
[227] A. J. Gotch, A. W. Garrett, T. S. Zwier, *J. Phys. Chem.* **1991**, *95*, 9699.
[228] B.-M. Cheng, J. R. Grover, E. A. Waiters, *Chem. Phys. Lett.* **1995**, *232*, 364.
[229] C. A. Hunter, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1584.
[230] J. M. Steed, T. A. Dixon, W. Klemperer, *J. Chem. Phys.* **1979**, *70*, 4940.
[231] S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497.
[232] C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Chem. Soc. Perkin Trans. 2* **2001**, 651.
[233] H. Gardarsson, W. B. Schweizer, N. Trapp, F. Diederich, *Chem. Eur. J.* **2014**, *20*, 4608.
[234] K.-T. Tang, J. P. Toennies, *Angew. Chem. Int. Ed.* **2010**, *49*, 9574; *Angew. Chem.* **2010**, *122*, 9768.
[235] R. P. Feynman, *Six easy pieces*, Basic Books, Philadelphia, **1963**.
[236] R. P. Feynman, *Caltech Eng. Sci.* **1960**, *23*, 22.
[237] a) L. A. Curtiss, K. Raghavachari, G. W. Trucks, J. A. Pople, *J. Chem. Phys.* **1991**, *94*, 7221; b) L. A. Curtiss, P. C. Redfern, K. Raghavachari, *J. Chem. Phys.* **2007**, *126*, 084108.

Received: April 16, 2015