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Evidence for the encounter complex in frustrated Lewis pair chemistry

Andrew R. Jupp 

Frustrated Lewis Pairs (FLPs) are combinations of bulky Lewis acids and bases that can carry out small-molecule activation and catalysis. Mechanistically, the reaction of the acid, base and substrate involves the collision of three distinct molecules, and so the pre-association of the acid and base to form an encounter complex has been proposed. This article will examine the evidence for the formation of this encounter complex, focusing on the archetypal main-group combinations $P(\text{tBu})_3/B(\text{C}_6\text{F}_5)_3$ and $\text{PMe}_3/B(\text{C}_6\text{F}_5)_3$ (Mes = mesityl), and includes quantum chemical calculations, molecular dynamics simulations, NMR spectroscopic measurements and neutron scattering. Furthermore, the recent discovery that the associated acid and base can absorb a photon to promote single-electron transfer has enabled the encounter complex to also be studied by UV-Vis spectroscopy, EPR spectroscopy, transient absorption spectroscopy, and resonance Raman spectroscopy. These data all support the notion that the encounter complex is only weakly held together and in low concentration in solution. The insights that these studies provide underpin the exciting transformations that can be promoted by FLPs. Finally, some observations and unanswered questions are provided to prompt further study in this field.

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Introduction

Combinations of a Lewis acid and a Lewis base typically form adducts *via* a dative bond, as described by Gilbert Lewis in his seminal work almost 100 years ago.¹ Several exceptions to this general rule have been found in the intervening years. In 1942, Brown and co-workers observed that 2,6-lutidine and BMe_3 do not form a Lewis adduct due to “steric interference”,² and there are subsequent examples of non-quenching pairs of acids and bases reacting with unsaturated substrates.^{3,4} However, it was the discovery by Stephan and co-workers in 2006 of a molecule containing discrete Lewis acidic and basic sites that could reversibly activate dihydrogen that demonstrated the true potential of these systems.⁵ The following year, the term “Frustrated Lewis Pair” (FLP) was coined⁶ to describe this general concept of a combination of a bulky Lewis acid and Lewis base that is sterically precluded from forming a Lewis adduct.⁷ The unquenched reactive acidic and basic sites in FLPs have been exploited for a wide range of small-molecule activation and catalysis, and this concept has inspired research groups around the world to explore metal-free approaches to reactions that were once considered the preserve of transition metal complexes.^{8–13} These reactions include the capture of environmentally relevant small molecules such as CO_2 , N_2O , and SO_2 ;^{14–17} the catalytic hydrogenation of unsaturated organic substrates;^{18–20} and C–H activation.²¹

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK. E-mail: a.jupp@bham.ac.uk

**Andrew R. Jupp**

Andy obtained his Ph.D. (2012–2016) from the University of Oxford under the supervision of Prof. Jose Goicoechea, working on phosphorus analogues of the cyanate anion and urea. He subsequently carried out a Banting Postdoctoral Fellowship with Prof. Doug Stephan at the University of Toronto (2016–2018), working on frustrated Lewis pairs (FLPs) and the functionalisation of CO_2 . In 2018, he became an NWO VENI

laureate at the University of Amsterdam, working with Prof. Chris Slootweg on the formation of main-group radicals in FLP systems. In 2020, he launched his independent career as a Birmingham Fellow at the University of Birmingham (UK), working on small-molecule activation and molecular photo-switches. He started a Royal Society University Research Fellowship in January 2021.



Mechanism for FLP reactivity

The mechanism for the FLP activation of small molecules like dihydrogen has been widely discussed.^{22,23} The splitting of H₂ by the cooperative action of a Lewis acid and Lewis base is a three-component reaction. Although termolecular reactivity is known in the literature,^{24,25} the probability of the acid, base and substrate colliding at the same time in the correct orientation for activation is low, and as such the pre-association of two of the three components has been proposed to explain the facile and rapid reactivity of FLPs (Scheme 1).

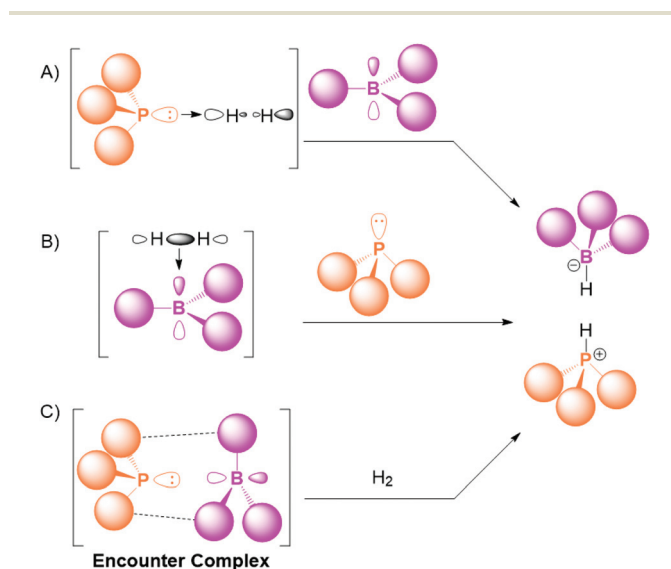
The Lewis base can theoretically interact with the substrate (typified by H₂ in Scheme 1A), and phosphine...H₂ interactions have been postulated in an argon matrix.²⁶ However, for the case of P^t(Bu)₃ with H₂, the interaction is computed to be repulsive in the chemically relevant range.²⁷ For certain small-molecule substrates like CO₂, the initial base...substrate interaction is more of a possibility, and strong Lewis bases such as N-heterocyclic carbenes and imidazolin-2-ylidene-amino-phosphines have been shown to bind CO₂.^{28–31} Scheme 1B shows the next alternative, where the substrate is initially bound to the Lewis acid. This pathway is well established for certain substrates; for example, the B(C₆F₅)₃-catalysed hydrosilylation of aromatic ketones, aldehydes and esters by Piers and co-workers,³² where the borane activates the silane moiety,³³ is regarded as an early example of FLP chemistry.³⁴ Furthermore, an alkene...borane adduct has been observed at low temperature as an intermediate in FLP activation,³⁵ and the zwitterionic adduct of B(C₆F₅)₃ with an alkyne was structurally characterised recently.³⁶ Regarding dihydrogen as the substrate, H₂ has been shown to bind to BH₃ in an argon matrix;³⁷ HB(C₆F₅)₂ can undergo σ -bond metathesis with H₂;³⁸ and antiaro-

matic boroles have been shown to activate H₂.^{39,40} However, calculations suggest that the interaction of H₂ with B(C₆F₅)₃ is unfavourable due to Pauli repulsion.²⁷

Therefore, particularly for the activation of H₂ with the prototypical FLP combinations of P^t(Bu)₃/B(C₆F₅)₃ or PMes₃/B(C₆F₅)₃ (Mes = mesityl), the prevailing theory is that depicted in Scheme 1C, where there is a pre-association of the bulky phosphine and base. This adduct is commonly referred to as the encounter complex, and is held together by weak van der Waals interactions between the substituents on the phosphine and borane. Understanding the nature of the encounter complex and the factors that affect its formation are critical to rationalising and optimising subsequent FLP reactivity, and a great deal of work has gone into studying this ephemeral species. The fact that the adduct is only weakly held together limited the studies of the encounter complex in the early days of FLP chemistry to computational investigations, but recent developments have gleaned key information using a range of experimental techniques, including NMR spectroscopy, UV-Vis spectroscopy, EPR spectroscopy, transient absorption spectroscopy, resonance Raman spectroscopy, and neutron scattering. These experimental breakthroughs are the focus of this Frontier article.

It is worth noting at this stage that there are alternative strategies for enhancing the pre-organisation of the acid and base moieties in FLPs. The most widely employed approach is tethering the two components with a covalent linker, known as an intramolecular FLP. Erker's ethylene-bridged FLP, Mes₂PCH₂CH₂B(C₆F₅)₂, is a pioneering example of such a system.⁴¹ Many different covalent linkers have been employed in the ensuing years, and selected examples of intramolecular FLPs include a simple methylene-bridged P/B system;⁴² a dimethylxanthene-bridged system that enables the reversible capture of N₂O;⁴³ a phenylene bridged N/B system that could catalyse the selective Z-reduction of alkynes;⁴⁴ a geminal S/B species that could be activated by light;⁴⁵ and even chiral systems for asymmetric catalysis.^{46–48} An alternative approach is for the acid and base to interact in a classical manner; there are a number of systems that are capable of FLP-type reactivity where the Lewis acid and base interact *via* a dative bond. Examples of these systems include combinations of the Lewis acid B(C₆F₅)₃ with 2,6-lutidine,⁴⁹ Et₂O,⁵⁰ 1,4-dioxane,⁵¹ or the proazaphosphatane P(N(Me)CH₂CH₂)₃N,⁵² where the classical adduct is in equilibrium with the dissociated acid and base.

However, this article will focus on the computational and experimental evidence for the presence of the encounter complex between discrete Lewis acids and bases to explain the termolecular reactivity of FLPs. There are a very large number of possible Lewis acids and bases; there have been interesting studies looking at N-heterocyclic carbene/borane combinations, although a large proportion of these systems either form a normal Lewis adduct or undergo a range of decomposition pathways *via* C–H or C–F activation, which limits the possibility of studying the encounter complexes in these systems experimentally.^{53–55} Recently, the trioxatriangulenium ion was explored as a carbon-centred Lewis acid in FLP chem-



Scheme 1 Mechanisms for the splitting of H₂ by an FLP comprising a bulky phosphine and borane as alternatives to true termolecular reactivity. A: pre-association of the phosphine and H₂; B: pre-association of the borane and H₂; and C: pre-association of the phosphine and borane as an encounter complex.



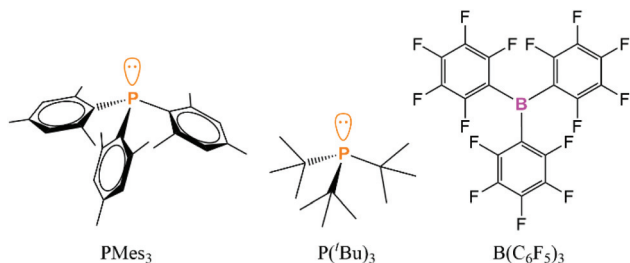


Fig. 1 The phosphines and borane in the prototypical encounter complexes that are the focus of this article.

istry, and the association with different phosphines was probed.⁵⁶ To focus the discussion and explore the evidence for the encounter complexes in more detail, the FLPs in this article will be limited to $P(tBu)_3/B(C_6F_5)_3$ or $PMe_3/B(C_6F_5)_3$ (Fig. 1), as these are the most commonly used FLPs and have significance in a wide range of catalytic applications.

Computational models of the encounter complex

The original research into the encounter complex was computational in nature. A seminal report from Pápai and co-workers first suggested the formation of the encounter complex in FLP chemistry.²⁷ They identified a weakly associated $[P(tBu)_3] \cdots [B(C_6F_5)_3]$ adduct as a minimum on the potential energy surface, using both B3LYP and SCS-MP2 methods. There was no evidence of charge transfer from the phosphine lone pair into the vacant orbital on boron, as shown by the planarity of the central BC_3 unit in $B(C_6F_5)_3$. Furthermore, the $P \cdots B$ distance at the energetic minimum was 4.2 Å (for the SCS-MP2 calculation); for comparison, the sum of the covalent radii would predict a P–B bond length of 1.96 Å in a Lewis adduct.⁵⁷ Instead, the adduct is stabilised by a combination of multiple C–H \cdots F non-covalent interactions, and in the absence of any solvent modelling the association energy was calculated as $\Delta E_{\text{assoc}} = -11.5 \text{ kcal mol}^{-1}$. The nature of the encounter complex being stabilised by many weak dispersion interactions means that there is a degree of structural flexibility, and it was shown that large changes in the $P \cdots B$ distance can be achieved at a relatively small energetic cost.

The significance of dispersion interactions to stabilise the encounter complex was also supported by a number of other studies.^{55,58,59} Note that there are contrasting theories for the mechanism of the activation of dihydrogen by the FLP.⁶⁰ Pápai proposed an electron transfer mechanism based on synergistic interactions of the donor and acceptor orbitals on the base and acid with the acceptor and donor orbitals on dihydrogen, respectively,^{27,61} whereas Grimme has proposed an electric field model, where the H–H bond is polarised by a strong electric field generated between the donor/acceptor atoms.^{58,62} A more recent publication has sought to unify these two mechanisms,⁶³ and very recently, Fernández and co-workers have

explored the activation strain model-energy decomposition analysis as a tool to probe reactivity in FLPs.^{64,65} Crucial to these theories is the formation of the pre-organised encounter complex stabilised by weak dispersion interactions with a reactive “pocket” available for the small-molecule substrate to be activated.

A further computational study by Vankova and co-workers corroborated the formation of the encounter complex is energetically favourable, with an average association energy across a range of systems of $\Delta E_{\text{assoc}} = -10 \text{ kcal mol}^{-1}$.⁶⁶ Incorporating solvent effects (toluene) using a polarisable continuum model led to only small changes in the association energy (less than 1 kcal mol^{-1}). However, the favourable electronic interactions in the encounter complex are counterbalanced by the entropic cost of adduct formation. Entropy is the dominant factor at room temperature, and the formation of the encounter complex is endergonic ($\Delta G_{\text{assoc}} = +5 \pm 2 \text{ kcal mol}^{-1}$), which is consistent with the difficulty in observing these species in the laboratory.⁶⁶

To move beyond the static computational models used in quantum chemical calculations, Pápai and co-workers used molecular dynamics (MD) simulations to probe the encounter complex of $P(tBu)_3/B(C_6F_5)_3$ in toluene.⁶⁷ The model system comprised one borane, one phosphine, and 1011 toluene molecules in a periodically repeated cell, which represents a relatively dilute solution compared to a typical experimental set-up. The Helmholtz free energy curve (see $F(r)$ in Fig. 2) showed that the formation of the encounter complex is disfavoured; the structures with a $P \cdots B$ distance in the chemically useful range of 4.2–5.6 Å were approximately 1.2 kcal mol^{-1} higher in energy than the dissociation limit. The probability of finding a configuration with a $P \cdots B$ distance of less than 6 Å (see $C(r)$ curve in Fig. 2 for cumulative probability of $P(r)$) was calculated to be roughly 2%, and those configurations featuring the optimal $P \cdots B$ distance of 4.5 Å were only present 0.5% of the time.

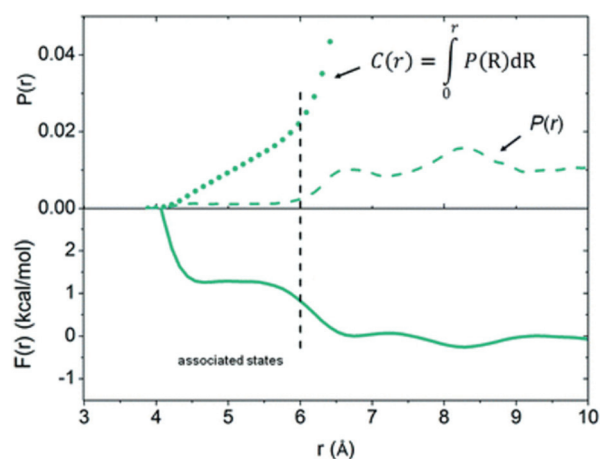


Fig. 2 Free energy curve, $F(r)$, and probability distribution, $P(r)$, computed from MD simulations of $P(tBu)_3/B(C_6F_5)_3$ in toluene. Reproduced from ref. 67 with permission from the Royal Society of Chemistry.



Experimental evidence for the encounter complex

Initial observation attempts

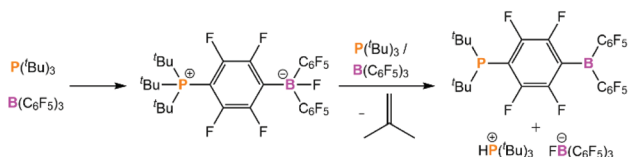
The weak stabilisation of the encounter complex in solution hampered early attempts to observe this species experimentally. It was reported that equimolar benzene or toluene solutions of $P(^t\text{Bu})_3/B(\text{C}_6\text{F}_5)_3$ or $\text{PMes}_3/B(\text{C}_6\text{F}_5)_3$ gave no indication of any interactions by ^1H , ^{11}B , ^{19}F , or ^{31}P NMR spectroscopy, and in each case the NMR spectra for the FLP looked the same as those of the individual components.^{7,68} Furthermore, isothermal reaction calorimetry performed by Houghton and Autrey revealed that no appreciable heat was produced on mixing PMes_3 and $B(\text{C}_6\text{F}_5)_3$ in dichloromethane.⁶⁹ This detailed calorimetric study concluded that the activation of H_2 by this FLP is best modelled as a termolecular reaction with a rate-determining step of assembling the reactants into the solvent cage in the correct configuration.

A further complication for exploring the encounter complex experimentally is that for one of the FLP combinations that we are discussing, $P(^t\text{Bu})_3/B(\text{C}_6\text{F}_5)_3$, there is a competing side-reaction between the two components to form the ion pair $[\text{HP}(^t\text{Bu})_3][\text{FB}(\text{C}_6\text{F}_5)_3]$ and the intramolecular species $(^t\text{Bu})_2\text{P}(\text{C}_6\text{F}_4)\text{B}(\text{C}_6\text{F}_5)_2$ with elimination of isobutylene (Scheme 2).⁷⁰ However, despite these hurdles, there have been some recent breakthroughs in the characterisation of the encounter complex that will be explored below.

NMR spectroscopy

The first report with unequivocal experimental evidence in support of the encounter complex was a comprehensive NMR spectroscopic study by Rocchigiani *et al.*⁶⁸ They performed ^{19}F , ^1H HOESY (Heteronuclear Overhauser Enhancement Spectroscopy) experiments on concentrated (220–230 mM) samples of $P(^t\text{Bu})_3/B(\text{C}_6\text{F}_5)_3$ or $\text{PMes}_3/B(\text{C}_6\text{F}_5)_3$ in benzene or toluene, and clear cross-peaks corresponding to H/F interactions could be observed (Fig. 3). Furthermore, addition of a substoichiometric amount of $B(\text{C}_6\text{F}_5)_3$ to a concentrated solution of PMes_3 (relative ratio phosphine:borane of 57:1) resulted in marginal shifts of the ^{19}F resonances relative to the free borane, and substantial line-broadening of the *para*-F. The temperature-dependent broadening of the ^{19}F NMR resonances of $B(\text{C}_6\text{F}_5)_3$ in the presence of excess PMes_3 at low temperature but not as the free borane is also consistent with aggregation of the phosphine and borane in solution.

The study also explored the relative orientation of the phosphine and borane in this aggregate to ascertain if there was



Scheme 2 Possible side-reaction between $P(^t\text{Bu})_3$ and $B(\text{C}_6\text{F}_5)_3$.

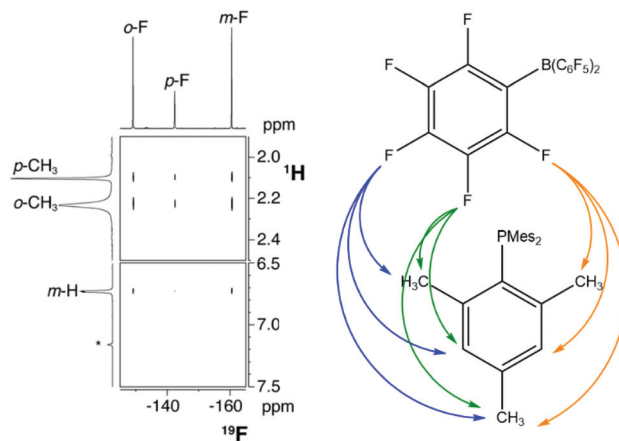


Fig. 3 ^{19}F , ^1H HOESY NMR spectrum of $\text{PMes}_3/B(\text{C}_6\text{F}_5)_3$ in benzene- d_6 , showing cross-peaks arising from all fluorine and proton environments. Adapted with permission from ref. 68. Copyright 2014 American Chemical Society.

any preferred directionality. The kinetics of NOE build-up and a comparison of the relative strengths of the NOEs within $\text{PMes}_3/B(\text{C}_6\text{F}_5)_3$ with computational predictions strongly indicate that the two components have a random relative orientation. This result suggests that the aggregation of the acid and base in solution is dominated by intramolecular H/F interactions, and not due to donation of the phosphine lone pair into the vacant p orbital on the borane. This hypothesis was corroborated with computations that revealed there was only 1 kcal mol⁻¹ between the two limiting structures of $\text{PMes}_3/B(\text{C}_6\text{F}_5)_3$ shown in Fig. 4, and the two extremes were roughly equally likely to exist in solution. Grimme and co-workers carried out a comprehensive computational investigation to explore this further using state-of-the-art quantum chemistry methods, building on the NMR spectroscopic data, and extended the study to $P(^t\text{Bu})_3/B(\text{C}_6\text{F}_5)_3$.⁷¹ The authors highlighted the importance of accurately modelling the dispersion interactions, and showed that for $\text{PMes}_3/B(\text{C}_6\text{F}_5)_3$ there is little energetic difference between the two extreme orientations depicted in Fig. 4 across a range of different methods, in agreement with experiment. However, for $P(^t\text{Bu})_3/B(\text{C}_6\text{F}_5)_3$, the orientation labelled geometry a in Fig. 4 is energetically favoured by 3–5 kcal mol⁻¹ (or 1–2 kcal mol⁻¹ in free energies) compared to geometry b, indicating that the association is less

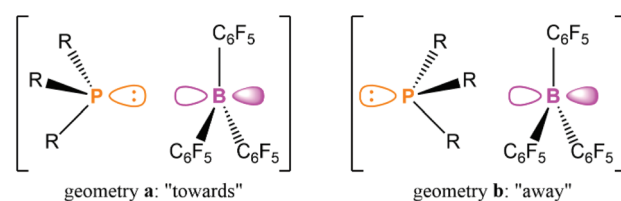


Fig. 4 The two limiting geometries for the association of a phosphine with $B(\text{C}_6\text{F}_5)_3$, with the P lone pair oriented "towards" or "away" from the p orbital on B.



driven by dispersion interactions, and that there is a small amount of P...B bonding present. This non-negligible P...B interaction in $P^t(Bu)_3/B(C_6F_5)_3$ has previously been discussed in terms of the frontier orbitals.⁷²

Rocchigiani and co-workers quantified the propensity of $PMes_3/B(C_6F_5)_3$ to associate in solution using diffusion ^{19}F and 1H NMR spectroscopy; the average association constant was determined to be $K = 0.5 \pm 0.2 M^{-1}$, meaning that formation of the encounter complex is slightly endergonic ($\Delta G^\circ = +0.4 \pm 0.2 \text{ kcal mol}^{-1}$). These results are consistent with the previously discussed data from molecular dynamics simulations.⁶⁷

More recently, Swadźba-Kwaśny and co-workers carried out further NMR experiments on the FLP combination $P^t(Bu)_3/B(C_6F_5)_3$.⁷³ Interestingly, their data show a clear change in the chemical shifts of the ^{19}F NMR resonances of free $B(C_6F_5)_3$ in benzene- d_6 versus the same resonances in a 1:1 mixture of $P^t(Bu)_3/B(C_6F_5)_3$ in benzene- d_6 , consistent with a small amount of P...B interaction. In a bid to determine whether ionic liquids can increase the concentration of the encounter complex in solution, they also carried out the same analysis of $P^t(Bu)_3/B(C_6F_5)_3$ using the ionic liquid $[C_{10}mim][NTf_2]$ as the solvent (Fig. 5). The ^{19}F NMR chemical shifts of free $B(C_6F_5)_3$ are significantly different when dissolved in $[C_{10}mim][NTf_2]$ compared to benzene- d_6 , consistent with interaction of the Lewis acidic borane with one of the components of the ionic liquid. There are undoubtedly new ^{19}F and ^{31}P NMR resonances that appear when $P^t(Bu)_3/B(C_6F_5)_3$ is dissolved in $[C_{10}mim][NTf_2]$ compared to the individual components; according to the study, 24% of the $B(C_6F_5)_3$ is no longer “free” (and this 24% is split across at least three different environments), while 78% of the $P^t(Bu)_3$ is also in a new environment. The authors state that although it is not possible to make definitive assignments for these new resonances, they could be attributed to the interaction between the FLP components in the encounter complex, which is stabilised to a greater extent in the ionic liquid compared to benzene- d_6 . This notion was explored computationally in a further MD study by Liu and co-workers, comparing the association of $P^t(Bu)_3/B(C_6F_5)_3$ in toluene and a range of ionic liquids.⁷⁴ They showed that in general the ionic liquids led to an enhanced probability of the phosphine and borane being associated with each other; the computed probability of finding $P^t(Bu)_3/B(C_6F_5)_3$ with a P...B distance of $\leq 6 \text{ \AA}$ in toluene was 2.32% (similar to the previously discussed value of 2% (ref. 67)), whereas this probability increased to 4.75–5.15% in the majority of the ionic liquids probed. For one of the ionic liquids, specifically

$[C_6mim][CTf_3]$, the same probability actually decreased to 1.08%, reflecting a decreased stability of the encounter complex in this case, so careful consideration of the nature of the ionic liquid is required. The authors propose that the ionic liquids pack together and leave large cavities that the encounter complex can accommodate, whereas toluene molecules move in between and separate the acid and base. These articles highlight the potential of ionic liquids as a tool to better study the encounter complex in FLP chemistry, although further work is required to unambiguously identify the encounter complex in these systems.

Neutron scattering

Swadźba-Kwaśny and co-workers also explored the nature of the association of $P^t(Bu)_3/B(C_6F_5)_3$ using neutron scattering experiments.⁷³ Neutron diffraction has previously been used to study structure and solvation,⁷⁵ and when combined with empirical potential structure refinement (EPSR) models can provide insight into complex systems. The measurements were carried out on equimolar solutions in benzene at 160 mmol concentration, which is relatively low for standard neutron scattering experiments, and resulted in poor resolution for the specific P...B interactions and significant variability between different refinement runs. Nevertheless, data could be obtained that provided evidence for association of the phosphine and borane molecules in solution. There was <1% chance of finding the $P^t(Bu)_3/B(C_6F_5)_3$ with a P...B distance of 5.7 \AA , but this increased to 4.9% chance at P...B separations of <8 \AA . These data are consistent with the weak association of the acid and base in solution, and highlight the utility of neutron diffraction for directly observing the encounter complex.

Equivalence with the electron donor–acceptor complex

Recent experimental evidence for the encounter complex has arisen from the blossoming field of frustrated radical pairs.^{76–79} The single-electron transfer (SET) from the Lewis base to the Lewis acid to form the radical pair was first postulated by Piers and co-workers, although it was discounted as a viable mechanism in FLP chemistry due to the large discrepancy in redox potentials between $P^t(Bu)_3$ and $B(C_6F_5)_3$.⁸⁰ A breakthrough from Stephan and co-workers was published in 2017, where they studied the FLP combination $PMes_3/B(C_6F_5)_3$ and saw evidence of the radical cation $[PMes_3]^+$, and postulated that the radical ion pair is in thermal equilibrium with the phosphine and borane.⁷⁶ The $[PMes_3]^+$ could be observed by EPR spectroscopy, although the corresponding $[B(C_6F_5)_3]^-$ radical was not observed, and this was attributed to the known and rapid decomposition of this radical anion *via* solvolytic pathways.^{81,82}

In light of the contradictory evidence above, Slootweg and co-workers sought to better understand the SET process in FLPs.^{83,84} Mulliken theory describes the interaction of an electron-rich donor (D) and an electron-poor acceptor (A) to form an electron donor–acceptor complex $[D,A]$, which can subsequently absorb a photon of the correct energy to promote

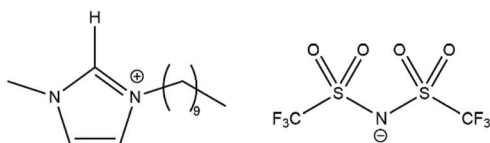


Fig. 5 Structure of ionic liquid $[C_{10}mim][NTf_2]$.



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