

# The solvent effect on the Diels–Alder reaction in ionic liquids: multiparameter linear solvation energy relationships and theoretical analysis

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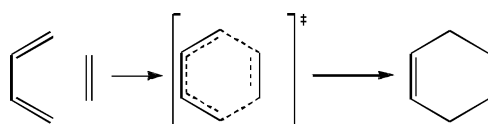
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This review illustrates how ionic liquid properties can affect Diels–Alder reactions. The mechanisms by which ionic solvents enhance the rate and selectivity of the reaction are discussed on the basis of correlation studies using empirical parameters and theoretical calculations.

## Introduction

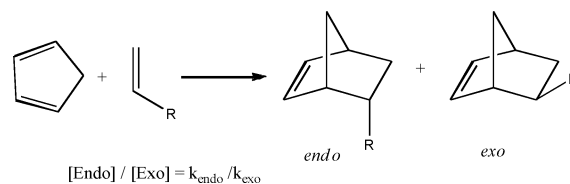
The Diels–Alder reaction (a 4 + 2 addition arising from the fusion of a diene with an alkene, generally defined as a dienophile; Scheme 1) is a powerful tool in organic synthesis and industrial chemistry as it permits the construction in one stage of the six-membered carbocycles contained in important compounds applied in drug delivery, biochemical applications, material sciences and devices.<sup>1</sup>



Scheme 1 The Diels–Alder reaction

The reaction is stereospecific in the sense that configurations of the reacting double bonds are fully retained in the

configuration of the product and the configuration of the two newly-formed asymmetric centers can be controlled efficiently. After a long debate on the concertedness of the Diels–Alder reaction,<sup>2</sup> a consensus has been reached in favor of the concerted mechanism; although concertedness does not imply that, in the activated complex, the extent of formation of the two new  $\sigma$ -bonds is necessarily the same.<sup>3</sup> When substituted dienes and dienophiles are employed, two different cycloadducts, denoted as *endo* and *exo*, are formed; under usual conditions, their ratio is kinetically controlled (Scheme 2).



Scheme 2 *Endo:exo* selectivity in Diels–Alder reactions

Fukui's frontier molecular orbital (FMO) theory has been shown<sup>4</sup> to be a valuable tool for predicting the rate and selectivity of pericyclic reactions and cycloadditions. This theory has also

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Cinzia Chiappe

Prof. Chiappe's primary interests are in using the tools of physico-organic chemistry to obtain information on ionic liquids and their solvent properties for developing new classes of sustainable ionic compounds; preferentially, starting from low cost renewable materials.

Cinzia Chiappe received *Laurea (cum laude)* and PhD degrees from the University of Pisa, Italy, in 1985 and 1989, respectively. After a two year period at the Regional Agency for Environmental Protection, she moved to the Department of Bioorganic Chemistry (University of Pisa) as a researcher. Since 2002, she has been a Full Professor of organic chemistry at the University of Pisa (Dipartimento di Chimica e Chimica Industriale).



Marco Malvaldi

Dr Malvaldi is performing chemical research for his own interest.

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been used to estimate reactivity and stereoselectivity in Diels–Alder reactions, which are considered to proceed under orbital control.

Many textbooks refer to the Diels–Alder cycloaddition as a typical example of a reaction that is indifferent towards the choice of the solvent. This is only strictly true for the very special case of Diels–Alder reactions between two purely hydrocarbon reactants, such as cyclopentadiene dimerization.<sup>5</sup> Actually, Diels–Alder reactions proceed at an appreciable rate only when either the diene or the dienophile are activated by an electron donating or electron withdrawing group, normally characterized by the presence of a heteroatom that can therefore efficiently interact with the solvent.

The influence of the solvent on these latter reactions has been extensively investigated, in particular after Breslow and Rideout<sup>6</sup> in 1980 evidenced the dramatic accelerating effect exerted by water.

Linear correlations between a reaction property (generally, reaction rate or *endo/exo* selectivity) and one or more solvent parameters (linear free energy relationship) or, more recently, *ab initio* calculations and computer simulations, have been used to obtain information on which solvent interactions play a major role. The acceptor number (AN), describing the ease with which the solvent can act as an electron pair acceptor, was considered<sup>7</sup> by Desimoni *et al.* as the dominant effect, at least on a specific kind of Diels–Alder reaction. The solvent–substrate interaction has been used subsequently by the same authors to classify<sup>8</sup> Diels–Alder reactions into three categories. First, Diels–Alder reactions of type A, which are characterized by an increase of the rate constant on increasing the AN power of the solvent. This behavior has been attributed to LUMO<sub>solvent</sub>–HOMO<sub>solute</sub> interactions and considered similar to Lewis acid catalysis. Then, Diels–Alder reactions of type B, dominated by the electron donation ability of the solvent, which decreases the reaction rate by soft–soft interactions: HOMO<sub>solvent</sub>–LUMO<sub>solute</sub> interactions have been considered responsible for this effect. Finally, Diels–

Alder reactions of type C: this class includes all the reactions that show a small solvent effect (for example, cyclopentadiene dimerization). In this case, solvent–solvent interactions are dominant, and a correlation with the solvent ced ( $\delta_{\text{H}}^2$ ) may be found.

Actually, the cohesive energy density (ced, not to be confused with the internal pressure),<sup>9</sup> together with the solvent H-bond acidity ( $\alpha$ ), has been evidenced<sup>10</sup> to also affect Diels–Alder reactions of type A, whereas in the special case of intramolecular Diels–Alder reactions in highly viscous media, Firestone *et al.* have demonstrated<sup>11</sup> the importance of solvent density.

On the other hand, the accelerating effect of LiClO<sub>4</sub> in diethyl ether was attributed to the internal pressure, initially by Grieco *et al.*<sup>12</sup> and later by Kumar.<sup>13</sup> This view has, however, been criticized and alternative explanations based on Lewis acid catalysis by the lithium cation or on a more efficient stabilization of the Diels–Alder transition state (TS) by this highly polar medium have been suggested.<sup>14,15</sup> Nevertheless, the Lewis acidity of lithium in organic media has been assessed more recently by Desimoni *et al.*<sup>16</sup>

In conclusion, although a multitude of different interactions can contribute to the Diels–Alder reaction rate, depending on the solvent, diene and dienophile, it is generally accepted that, at least, the most extensively investigated Diels–Alder reactions of type A are dominated by hydrogen bond interactions in combination with solvophobic interactions, these latter interactions essentially being quantified by the ced. The hydrophobic component of the rate enhancement has been considered to be derived from the removal of solvent accessible non-polar surface area in the TS,<sup>17</sup> although the possibility that it should be a consequence of the complete disappearance of the hydrophobic character of the different groups near the reaction center in the dipolar and strongly hydrated activated complex has been advanced.<sup>18</sup>

These two parameters are also considered to determine the water effect. In terms of TS theory, hydrophobic hydration raises the initial state more than the TS and hydrogen bonding interactions stabilize the TS more than the initial state. Highly polarizable activated complexes play a key role in both of these effects.<sup>19</sup>

However, solvent also affects the *endo/exo* diastereofacial selectivity of Diels–Alder reactions. The hydrogen bond donor power of the solvent and its polarity<sup>20</sup> (together with its ability to induce hydrophobic interactions, in the case of water) have been considered the main factors favoring the formation of the *endo* adduct. Hydrophobic effects are assumed to stabilize the more compact *endo* TS than the extended *exo* TS.

Nevertheless, in the last 20 years, several physico-chemical methods have been tested to promote reluctant Diels–Alder reactions. These include the use of high pressure,<sup>21</sup> ultrasound irradiation,<sup>22</sup> catalysis through the formation of supermolecular assemblies (e.g. cyclodextrins,<sup>23</sup> or related basket-<sup>24</sup> or capsule-like<sup>25</sup> structures) or heterogeneous systems (clays, alumina or silica gel). By far the most effective method is generally considered to be catalysis by Lewis-acids; in organic solvents, accelerations in the order of 10<sup>4</sup> to 10<sup>6</sup>, normally accompanied by a considerable increase in selectivity, have been observed.<sup>26</sup>

Recently, the increased focus on the use of ionic liquids (ILs), organic salts liquid at or near room temperature, as



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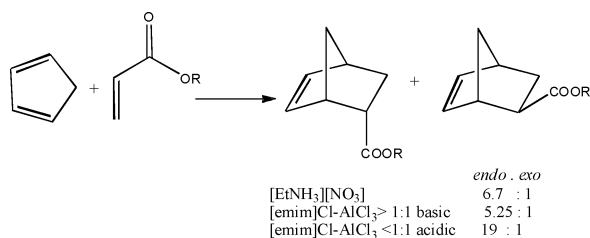
green solvents in synthetic organic chemistry has resulted in a significant number of investigations related to the use of these alternative media in Diels–Alder reactions.<sup>27</sup>

Kinetic and stereochemical investigations have been performed on model Diels–Alder reactions to evaluate the ability of ILs to affect *endo/exo* selectivity and reaction rate. The origins of ILs' solvent effect on this reaction are discussed in terms of solvent parameters and studied using computational methods.

The aim of this review is to present the various approaches that have been carried out to rationalize the ability of ILs to affect reactivity and selectivity, and, simultaneously, to use comparisons with the previously performed studies in molecular solvents to obtain information about the “distinctive” solvent properties of ILs.

### Effects of ionic liquids on Diels–Alder reactions

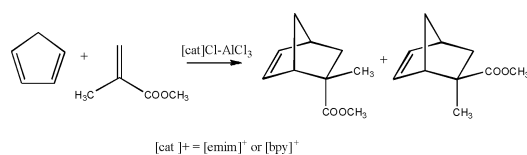
ILs, with their peculiar properties such as high polarizability/dipolarity, good hydrogen bond donor ability and high  $\epsilon$ , were straight away considered to have the potential to influence the outcome of Diels–Alder reactions.<sup>28</sup> The first investigation on the reaction between cyclopentadiene and alkyl acrylates in an IL was performed using ethylammonium nitrate which, surprisingly, gave a mixture of *endo* and *exo* products in a ratio of 6.7 : 1 (Scheme 3).<sup>29</sup> Since then, a number of examples of Diels–Alder reactions in different ILs have been reported. Chloroaluminate ILs have been used as both solvents and Lewis catalysts.<sup>30,31</sup>



**Scheme 3** Reactions of cyclopentadiene with alkyl acrylates.

When an acidic melt of 1-ethyl-3-methylimidazolium chloride–aluminium trichloride, [emim]Cl–AlCl<sub>3</sub> (51% AlCl<sub>3</sub>), was used as the solvent for the Diels–Alder reaction of cyclopentadiene and methyl acrylate, the experimental rate of reaction was 10, 175, and 560 times faster than in water, ethyl ammonium nitrate and 1-chlorobutane, respectively. However, the basic melt of [emim]Cl–AlCl<sub>3</sub> (48% AlCl<sub>3</sub>) gave a rate 2.4 times slower than that in water. *Endo* selectivity was also enhanced with a good yield when acidic [emim]Cl–AlCl<sub>3</sub> was used as the solvent; whereas the basic chloroaluminate IL gave an *endo* : *exo* ratio of 5.25 : 1; the acidic melt was characterized by a ratio of 19 : 1.

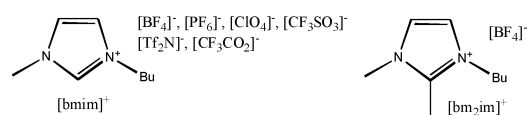
Analogously, the reaction of cyclopentadiene with methyl methacrylate, which is *exo*-selective in organic solvents (*endo* : *exo* ratio of 0.35 : 1), maintained the same selectivity in 45% AlCl<sub>3</sub>–butylpyridinium-chloroaluminate (45% AlCl<sub>3</sub>–[bpy]–chloroaluminate) and 45% AlCl<sub>3</sub>–[emim]–chloroaluminate, but became *endo*-selective in 60% AlCl<sub>3</sub>–[bpy]–chloroaluminate or 60% AlCl<sub>3</sub>–[emim]–chloroaluminate (Scheme 4).<sup>32</sup> Higher degrees of reversal in *endo* : *exo* ratio



**Scheme 4** The Diels–Alder reaction of cyclopentadiene with methyl methacrylate

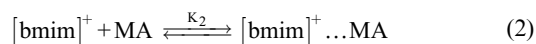
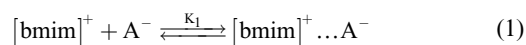
(4.5 : 1 with respect to 3 : 1) were obtained in 60% AlCl<sub>3</sub>–[emim]–chloroaluminate.

Subsequently, Welton *et al.* have investigated<sup>33</sup> the influence of non-chloroaluminate ILs on Diels–Alder reactions (Scheme 5). Most of the employed ILs were based on the 1-butyl-3-methylimidazolium cation, [bmim]<sup>+</sup>, although one example of an IL bearing a methylated cation at the 2-position of the ring, 1-butyl-2,3-dimethylimidazolium ([bm<sub>2</sub>im]<sup>+</sup>), was reported.



**Scheme 5** ILs used in the reaction of cyclopentadiene with methyl acrylate in ref. 33.

The *endo* : *exo* ratio and associated acceleration observed in the Diels–Alder addition of cyclopentadiene with methyl acrylate was attributed to the ability of the IL to hydrogen bond to the dienophile (methyl acrylate), a process considered to be determined by two competing equilibria. The IL cation ([bmim]<sup>+</sup>) can hydrogen bond to the anion of the IL (eqn 1) or to the methyl acrylate (eqn 2):

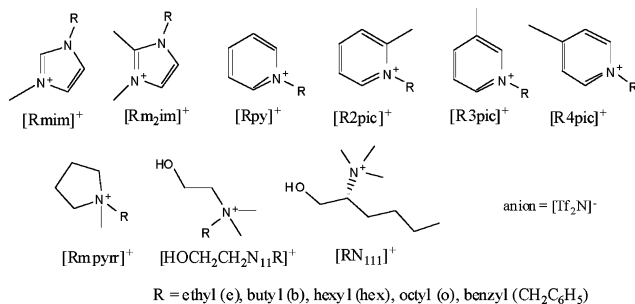


The concentration of the hydrogen-bonded cation–methyl acrylate adduct has been proposed to be inversely proportional to the equilibrium constant for the formation of the cation–anion hydrogen-bonded adduct ( $K_1$ ).

In light of the more recent data on IL structure,<sup>34</sup> it is, however, evident that this representation, although effective to support the role of both the cation and anion, is an oversimplification of the real situation. Eqn 1 represents the dissociation of an ion pair, but ILs should be described as a three-dimensional network of anions and cations, in which each ionic species is surrounded by several counterions. The interaction of the cation with reagents and/or the TS implies a reduction of the interactions of this cation with the surrounding anions. The dissolution of a substrate in a solvent, also including ILs, can be represented as follows: a “cavity” is created in the solvent to insert the substrate, and subsequently the reorganization and reorientation of the solvent around solute occurs.<sup>35</sup> In agreement with the system represented by eqn 1 and eqn 2, a strong interaction between IL cations and anions disfavors the formation of the cavity, and reduces the rate of reorganization and reorientation of cations and anions around the reagents, thus decreasing the possibility for the cation (or anion) to solvate the reagent and/or the TS. However, the situation is

much more complicated than that represented by eqn 1, eqn 2, involving a system more complex than an ion pair, and in which kinetic effects also play a role during the solvent reorganization and reorientation. The concept of ion pair association and dissociation, widely used for solutions of ionic compounds in molecular solvents, probably cannot be transferred as it stands to ILs.

More recently, Dyson *et al.* have investigated<sup>36</sup> the solvent effect on the same Diels–Alder reaction (cyclopentadiene–methyl acrylate) by extending the series of ILs: 1,2-dialkyl- and 1,2,3-trialkylimidazolium, alkylpyridinium, dialkylpyrrolidinium, 2-methyl, 3-methyl and 4-methyl alkylpyridinium (alkylpicolinium), and hydroxyalkylammonium bistriflimides have been used (Scheme 6). The *endo/exo* selectivities reported in this work are collected in Table 1, together with analogous data arising from other sources.



**Scheme 6** ILs used in the reaction of cyclopentadiene with methyl acrylate in ref. 36.

On the basis of kinetic measurements and product distribution studies, it has been found that strongly interacting groups, such as hydroxyl, carboxyl, nitrile or benzyl groups, on the IL cation increase the selectivity compared to alkyl chains. On the other hand, *endo* selectivity decreases upon increasing the alkyl chain length on the cation.

Surprisingly, at least considering the generally reported reduced ability of imidazolium salts bearing a methyl group at C2 to give hydrogen bonding,<sup>28</sup> 1-alkyl-2,3-dimethylimidazolium ILs gave selectivities (4.4 *endo:exo* ratio in [bm<sub>2</sub>im][Tf<sub>2</sub>N]) slightly higher than their 1-alkyl-3-methylimidazolium analogues (4.2 *endo:exo* ratio in [bmim][Tf<sub>2</sub>N]). This observation, in conjunction with the relatively high selectivities observed in *N*-alkylpyridinium and *N,N*-dialkylpyrrolidinium salts, suggested that the hydrogen bond donor ability of the cation does not satisfactory account for the observed selectivity.

It is, however, noteworthy that different values of selectivity have been reported for the reaction of methyl acrylate with cyclopentadiene in the same IL (see Table 1). These values generally range for dialkyl or trialkylimidazolium salts from 4.1 to 4.6. Although the choice of one value over another can lead to different conclusions,<sup>33,36</sup> it is necessary to consider that they correspond to very small variations in the product distribution, from 80 : 20 to 82 : 18, probably within the limit of experimental error.

Nevertheless, a correlation between the *endo:exo* ratio and some NMR spectroscopy-based empirical solvent parameters was attempted by Dyson *et al.*<sup>36</sup> The hydrogen bond donor capacity, steric bulk and overall polarity were identified as the

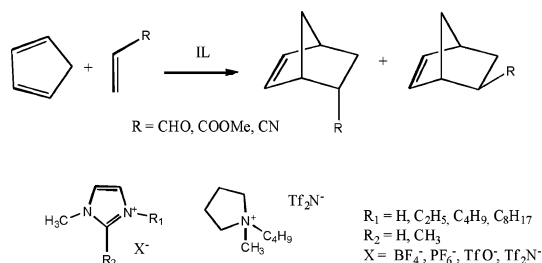
**Table 1** The selectivity of the reaction of cyclopentadiene with methyl acrylate in a variety of ILs and some molecular solvents

| IL  | <i>Endo:exo</i> | Ref. |
|---|-----------------|------|
| [EtNH <sub>3</sub> ][NO <sub>3</sub> ]                                    | 6.7             | 29   |
| [emim]Cl–AlCl <sub>3</sub> (48% AlCl <sub>3</sub> )                       | 5.25            | 30   |
| [emim]Cl–AlCl <sub>3</sub> (51% AlCl <sub>3</sub> )                       | 19              | 30   |
| [bmim]Cl–AlCl <sub>3</sub> (55% AlCl <sub>3</sub> )                       | 7.7             | 31   |
| [bmim]Cl–AlCl <sub>3</sub> (65% AlCl <sub>3</sub> )                       | 10.1            | 31   |
| [bmim][BF <sub>4</sub> ]  | 4.6             | 33   |
| [bmim][BF <sub>4</sub> ]  | 3.5             | 36   |
| [bm <sub>2</sub> im][BF <sub>4</sub> ]                                    | 3.3             | 33   |
| [bmim][ClO <sub>4</sub> ]   | 4.8             | 33   |
| [bmim][PF <sub>6</sub> ]  | 4.8             | 33   |
| [bmim][PF <sub>6</sub> ]  | 3.8             | 36   |
| [bmim][SbF <sub>6</sub> ]   | 4.2             | 36   |
| [bmim][OTf]   | 4.5             | 33   |
| [bmim][CF <sub>3</sub> COO]   | 4.0             | 33   |
| [bmim][CF <sub>3</sub> COO]   | 4.4             | 36   |
| [bmim][Tf <sub>2</sub> N]   | 4.3             | 33   |
| [bmim][Tf <sub>2</sub> N]   | 4.2             | 36   |
| [HO(CH <sub>2</sub> ) <sub>2</sub> mim][Tf <sub>2</sub> N]                | 6.1             | 33   |
| [CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> mim][Tf <sub>2</sub> N] | 5.7             | 33   |
| [Hmim][Tf <sub>2</sub> N]   | 6.1             | 37   |
| [mmim][Tf <sub>2</sub> N]   | 5.1             | 36   |
| [emim][Tf <sub>2</sub> N]   | 4.3             | 36   |
| [hexmim][Tf <sub>2</sub> N]   | 4.1             | 36   |
| [omim][Tf <sub>2</sub> N]   | 3.9             | 36   |
| [C <sub>3</sub> H <sub>6</sub> CO <sub>2</sub> Hmim][Tf <sub>2</sub> N]   | 5.4             | 36   |
| [C <sub>3</sub> H <sub>6</sub> CNmim][Tf <sub>2</sub> N]                  | 4.4             | 36   |
| [CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> mim][Tf <sub>2</sub> N]    | 5.1             | 36   |
| [em <sub>2</sub> im][Tf <sub>2</sub> N]                                   | 4.6             | 36   |
| [bm <sub>2</sub> im][Tf <sub>2</sub> N]                                   | 4.4             | 36   |
| [bm <sub>2</sub> im][Tf <sub>2</sub> N]                                   | 4.1             | 37   |
| [epy][Tf <sub>2</sub> N]  | 4.6             | 36   |
| [bpy][Tf <sub>2</sub> N]  | 4.1             | 36   |
| [hexpy][Tf <sub>2</sub> N]  | 4.1             | 36   |
| [opy][Tf <sub>2</sub> N]  | 4.0             | 36   |
| [CH <sub>2</sub> C <sub>3</sub> H <sub>6</sub> py][Tf <sub>2</sub> N]     | 4.6             | 36   |
| [e2pic][Tf <sub>2</sub> N]  | 4.2             | 36   |
| [b2pic][Tf <sub>2</sub> N]  | 3.9             | 36   |
| [CH <sub>2</sub> C <sub>3</sub> H <sub>6</sub> 2pic][Tf <sub>2</sub> N]   | 4.3             | 36   |
| [b3pic][Tf <sub>2</sub> N]  | 3.9             | 36   |
| [o3pic][Tf <sub>2</sub> N]  | 3.8             | 36   |
| [e4pic][Tf <sub>2</sub> N]  | 4.7             | 36   |
| [b4pic][Tf <sub>2</sub> N]  | 4.2             | 36   |
| [CH <sub>2</sub> C <sub>3</sub> H <sub>6</sub> 4pic][Tf <sub>2</sub> N]   | 4.8             | 36   |
| [HOCH <sub>2</sub> CH <sub>2</sub> N <sub>11</sub> ][Tf <sub>2</sub> N]   | 5.5             | 36   |
| [HOCH <sub>2</sub> CH <sub>2</sub> N <sub>14</sub> ][Tf <sub>2</sub> N]   | 5.1             | 36   |
| [HOCH <sub>2</sub> CH <sub>2</sub> N <sub>16</sub> ][Tf <sub>2</sub> N]   | 4.7             | 36   |
| [bmpyrr][Tf <sub>2</sub> N]   | 4.8             | 36   |
| [bmpyrr][Tf <sub>2</sub> N]   | 4.2             | 37   |
| [CH <sub>2</sub> C <sub>3</sub> H <sub>6</sub> mpyrr][Tf <sub>2</sub> N]  | 4.8             | 36   |

more relevant properties determining selectivity. With the aim of obtaining a better understanding of IL solvent properties, in collaboration with Welton's group, some of us have more recently re-investigated<sup>37</sup> Diels–Alder reactions in ILs (Scheme 7). A kinetic and product distribution study was carried out in nine ILs and some conventional organic solvents using three dienophiles with different hydrogen bond acceptor abilities: acrolein, methyl acrylate and acrylonitrile.

*Endo* selectivities, ranging from 2 to 4.8 (acrolein) or 6.1 (methyl acrylate) were obtained with both carbonyl-containing dienophiles, whereas lower values (ranging from 1 to 2.3) were characterized by acrylonitrile.

To analyze the influence of the solvent on the reaction rate and *endo/exo* selectivity, we tested linear regression models of  $\ln k_2$  and  $\ln(\textit{endo/exo})$  with some solvent parameters. Since attempts



**Scheme 7** The investigated dienophiles and ILs in ref. 37.

to correlate the *endo/exo* selectivities and the kinetic constants to solvent properties using single parameter relationships gave (with few exceptions) fairly poor correlations, the multilinear relationship (LSER) approach, initially introduced by Kamlet, Abboud and Taft,<sup>38</sup> and subsequently developed by Abraham,<sup>39</sup> describing solvation effects in terms of nonspecific and specific interactions, was used to correlate the *endo/exo* selectivities or kinetic constants to the solvent properties. Selectivity and reaction rate were modelled using linear free energy relationships based on the combination of the following parameters:  $\alpha$  and  $\beta$ , measuring, respectively, the solvent hydrogen bond donor acidity and acceptor basicity,  $\pi^*$ , an index of solvent dipolarity/polarizability,  $\Delta U_v$ , the internal energy of the solvent,  $V_M$ , the solvent molar volume,  $\delta^2$ , solvent ced,  $\eta$  solvent viscosity and  $E_T^N$ , the Reichardt electrophilicity, which is generally a linear function of both  $\alpha$  and  $\pi^*$ ,<sup>40</sup> whereas  $\Delta U_v$  and  $V_M$  are related to ced by the well-known relationship  $\delta^2 = (\Delta U_v / V_M)^2$ .

In Table 2 are reported the LSERs that better describe the selectivities and reaction rates. The same Table also reports the best fit parameters arising from previous studies on the same reactions in molecular solvents. Unfortunately, the models previously proposed by Karpyak *et al.*<sup>41</sup> and Cavitiella *et al.*<sup>42</sup> include other solvent parameters, and the related experiments have not been performed under exactly identical conditions.

Consequently, a rigorous comparison between the different models is not possible. However, some peculiarities emerge from the comparison of the LSERs characterizing each substrate. Firstly, different combinations of solvent parameters must generally be used to describe the selectivity and reaction rate. This may be due to the fact that selectivity arises from the ratio  $k_{endo}/k_{exo}$ , whereas the overall rate of the reaction is the sum of two kinetic constants. As a consequence, some solvent effects are cancelled-out when selectivity is considered. For example, the viscosity is present in the correlation for  $\ln k_2$  for acrolein but it is absent in that of selectivity; this behaviour might be due to the fact that viscosity affects the reaction rate for the *endo* and *exo* adducts in the same manner. More difficult to rationalize are the parameters present in the correlations related to selectivity but not in those of reactivity!

Secondly, the addition of acrolein to cyclopentadiene is the process that, better than any other, can be described by this analysis. Both selectivity and reactivity data gave fairly good correlations using a relatively limited number of parameters. Moreover, the same parameters describing selectivity are also present in the reactivity correlation. In particular, the  $\alpha$  parameter determines the selectivity and strongly affects the reactivity. A very large acceleration was observed in 1-butylimidazolium bistriflimide ([Hbim][Tf<sub>2</sub>N]), where the highly polarised N–H bond on the cation favours a stronger hydrogen bond interaction between this IL and the carbonyl of acrolein. However, the increase in the second order rate of the Diels–Alder reaction between cyclopentadiene and acrolein is favoured not only by the  $\alpha$  parameter but also by solvent dipole/polarizability effects (positive coefficients for  $\alpha$  and  $\pi^*$ ), while detrimental contributions arise from solvent viscosity and hydrogen bond acceptor ability (negative coefficients for  $\beta$  and  $\eta$ ). The positive influence of the ability of the medium to interact through dipole/polarizability may be attributed to a stabilization of the TS relative to the reactants due to its more dipolar character.<sup>43</sup>

**Table 2** LSERs describing the solvent effect on the selectivity,  $\ln(\textit{endo/exo})$ , and rate,  $\ln k_2$ , of Diels–Alder reactions

|                                   | Acrolein  | Methyl acrylate   | Acrylonitrile   | Ref.     |
|-----------------------------------|---|---|---|----------|
| <b>ILs and molecular solvents</b> |   |   |   |          |
| $\ln(\textit{endo/exo})$          | $1.042 + 0.560\alpha + 0.116\pi^* - 3.929 \times 10^{-4}V_M$<br>$R^2 = 0.96$  | $0.936 + 0.515\alpha + 0.375\pi^* - 7.421 \times 10^{-4}\Delta U_v$<br>$R^2 = 0.964$  | $0.335 + 0.328E_T^N + 0.493\beta + 2.818 \times 10^{-3}\Delta U_v - 3.168 \times 10^{-3}V_M$<br>$R^2 = 0.949$   | 37       |
| $\ln k_2$                         | $-9.86 + 0.99\alpha - 1.53\beta + 1.34\pi^* - 0.002\eta$<br>$R^2 = 0.852$<br>$-9.77 + 2.94E_T^N - 1.53\beta - 0.002\eta$<br>$R^2 = 0.837$ | $-11.36 + 1.81E_T^N$<br>$R^2 = 0.691$<br>$-11.46 + 0.61\alpha + 0.91\pi^*$<br>$R^2 = 0.684$   | $-13.26 + 3.00\pi^*$<br>$R^2 = 0.903$   |          |
| <b>Molecular solvents</b>         |   |   |   |          |
| $\log(\textit{endo/exo})$         | $-0.605 - 0.82f(\epsilon) + 0.034E_T - 0.342 \times 10^{-3}\delta^2 + 0.26 \times 10^{-2}V_M$<br>$R = 0.986$                              | $-0.317 + 2.42 \times 10^{-2}E_T - 0.202 \times 10^{-3}\delta^2$<br>$R = 0.971$<br>$0.386 + 0.153\alpha + 0.133\pi^* + 0.432S_p$<br>$R = 0.997$ | $-0.205 - 0.107f(n^2) + 1.250f(\epsilon) + 0.107 \times 10^{-3}B + 0.172 \times 10^{-2}V_M$<br>$R = 0.96$<br>$0.07 + 0.15S_p + 0.16\pi^*$<br>$R = 0.93$ | 41<br>42 |
| $\log k_2$                        | $-3.89 + 6.69f(n^2) - 2.42f(\epsilon) + 0.11E_T - 1.30 \times 10^{-3}\delta^2$<br>$R = 0.957$   | $0.026 - 0.549f(\epsilon) + 0.042E_T - 0.84 \times 10^{-3}\delta^2$<br>$R = 0.96$<br>$-3.195 + 2.075S_p + 0.904E_T^N$<br>$R = 0.94$             | $-5.51 + 0.95S_p + 0.80\pi^* + 0.55\alpha$<br>$R = 0.96$  | 41<br>42 |

On the other hand, we cannot exclude that viscosity and the  $\beta$  parameter are related to the previously mentioned three dimensional effects, giving a measure of the facility of cation–anion reorganization and reorientation around the TS.

In molecular media, for the addition of acrolein to cyclopentadiene, the solvent effect on the *endo/exo* isomer ratio has been described by Karpyak *et al.*<sup>41</sup> using a four-parameter equation when the six-parameter equation reported below was applied:

$$\log(\textit{endo/exo}) = \alpha_0 + \alpha_1 \frac{\eta^2 - 1}{\eta^2 + 2} + \alpha_2 \frac{\epsilon - 1}{2\epsilon + 1} + \alpha_3 B + \alpha_4 E_T + \alpha_5 \delta^2 + \alpha_6 V_M$$

Here,  $n$  is the solvent refractive index,  $\epsilon$  its dielectric permittivity,  $B$  Palm basicity,  $E_T$  Reichardt electrophilicity,  $\delta^2$  the Hildebrand solubility parameter and  $V_M$  the molar volume. Considering that the Reichardt electrophilicity can be written as a linear function of both  $\alpha$  and  $\pi^*$ , the LSER equation presented by Karpyak agrees fairly well with the results obtained by applying the Abboud–Kamlet–Taft analysis to a system containing both ILs and molecular solvents: the hydrogen bond donor ability of the solvent ( $\alpha$ ) and the dipolarity/polarizability property of the solvent ( $\pi^*$ ) increase the *endo* adduct. Nevertheless, the inclusion of ILs seems to reduce the negative influence of polarity described by  $\epsilon$  and the positive influence of the terms for cohesive pressure and molar volume. On the other hand, more significant differences characterize the equations describing the solvent effect on the reaction rate of cyclopentadiene with acrolein reported by Karpyak, and more recently found for a system constituted by ILs and molecular solvents, which can be attributed, in part, to the different solvent parameters used and to the ILs' peculiarities.

The cycloaddition of cyclopentadiene to methyl acrylate is perhaps the most intensively studied Diels–Alder reaction and, although on many occasions it has been found that hydrogen bond interactions can enhance its *endo* selectivity, due to the presence of the carbonyl acceptor group on the dienophile, the reaction of methyl acrylate in ILs seems to be less affected by the  $\alpha$  parameter than the reaction of acrolein. Only in the case of ILs bearing hydroxyl groups or a highly polarised N–H bond (*i.e.* Brønsted acidic imidazolium-based ILs, such as [Hbim]<sup>+</sup>) is it possible to observe a significant increase in *endo* selectivity and reactivity, whereas a comparison between [bm<sub>2</sub>im][Tf<sub>2</sub>N] and its analogue [bmim][Tf<sub>2</sub>N] argues against the fact that the interaction expressed by  $\alpha$  can be the main factor in determining reactivity. This is also in agreement with the selectivity data previously discussed<sup>36</sup> and reported in Table 1. A possible reason for this behaviour may be found in the fact that other factors determine selectivity. For example, ILs such as [bm<sub>2</sub>im][Tf<sub>2</sub>N] and [bmpy][Tf<sub>2</sub>N], with lower hydrogen bonding abilities but higher cohesive pressures and polarity values, may give selectivities comparable to that of [emim][Tf<sub>2</sub>N] if these factors play a detectable role. The LSER reported in Table 2 supports this hypothesis, showing the high importance of both the hydrogen bond donor and dipolarity/polarizability properties of the solvent, together a smaller contribution from the internal energy term.

A decisive role of the electrophilic solvation of the solvent to the carbonyl group, together with the polarity of the medium, has also been reported<sup>41</sup> by Karpyak *et al.* as the main causes

determining the *endo* selectivity of the Diels–Alder reaction between cyclopentadiene and methyl acrylate in molecular solvents. On the other hand, a dependence of the *endo/exo* selectivity on the solvophobic, dipolarity/polarizability and hydrogen bond donor properties of the solvent was evidenced<sup>42</sup> by Cativiela *et al.* by analysing the selectivity of the same reaction in several solvents and organic–aqueous mixtures by means of regression models using empirical solvent parameters such as solvophobicity ( $S_p$ ), hydrogen bond donor ( $\alpha$ ), hydrogen bond acceptor ( $\beta$ ), dipolarity/polarizability ( $\pi^*$ ) and  $E_T^N$ .

Finally, there is the case of acrylonitrile, whose reactivity appears to be determined only by solvent polarizability/dipolarity, whereas selectivity requires a combination of several parameters:  $E_T^N$ , hydrogen bond basicity, molar volume and solute internal energy. It is notable that attempts to use  $\alpha$  and  $\pi^*$  instead of  $E_T^N$  failed, supporting the hypothesis that the correlation between  $E_T^N$  and its intrinsic parameters ( $\alpha$  and  $\pi^*$ ) does not work in ILs.

This may be due to the fact that the meaning of at least some of the solvatochromic parameters, such as  $E_T^N$ , may be not exactly the same in molecular and ionic solvents; more interactions could contribute to the solvatochromic effect measured in ILs.

As recently evidenced by Khupse and Kumar,<sup>44</sup> polarity data of ILs expressed by  $\alpha$ ,  $\beta$ ,  $\pi^*$  or  $E_T^N$  parameters showed features that were not observed earlier or were too “weak” to be observed in the case of conventional solvents. For example, ILs show, probably as a consequence of their ability to give highly ordered microsegregated phases in binary mixtures, a strong tendency towards the preferential solvation of a probe molecule in their binary mixtures with molecular solvents, which can result in unique synergistic effects.<sup>45</sup>

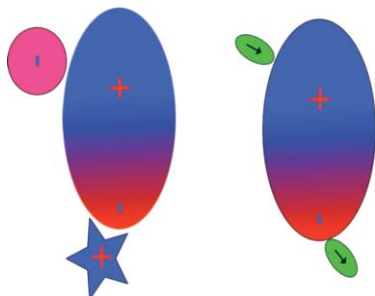
However, polarity parameters also show<sup>42</sup> a significant temperature dependence or “thermosolvatochromism”, which is generally a complex function of the cation and anion structure. The change of polarity with temperature in directions depending on the IL structure, never observed in molecular solvents, suggests a more sophisticated system of interactions in ionic media.

Surely, there are some issues related to the nature of ILs that can reduce the reliability of solvatochromic parameters determined in these media, especially those related to Reichardt's dye, a molecule having several steric and electronic requirements. The nature of physical interactions in molecular and ionic solvents is different: IL components carry more or less dispersed positive and negative charges. This dispersion can give rise to a net dipole and quadrupole moment that can significantly affect the detailed structure of the solvation shell. Thus, the dominant term in the interaction between ILs and solvatochromic probes becomes the charge–multipole, whereas dipole–dipole interactions are determinant in molecular solvents. Furthermore, generally, IL anions or cations present the same net charge, independent of their molecular geometry. In contrast, in molecular solvents, the dipole associated with each molecule is strictly correlated to its molecular geometry.

In the charge–dipole (or multipole) interaction, the most specific quantity is the distance between the two sources of potential. This quantity depends only on the shape of the molecule and not its charge distribution. Thus, it is a less specific parameter. Furthermore, usually, IL anions and cations are of

different shape and size and, generally, they are bigger than the molecules constituting molecular solvents. If the cation is smaller than the anion, it can reach a position in space closer to the solvatochromic probe and *vice versa*.

Considering specifically the case of Reichardt's dye, we can observe that this probe presents an easily accessible negative charge, at least when localized on oxygen, whereas the positive charge on the nitrogen is "buried" by its surrounding phenyl rings. Consequently, we can reasonably hypothesize that a cation will be strongly localized and interact with the negative charge. This interaction can take advantage from some of the chemical features of the cation, such as the availability of the hydrogen on C2 in [bmim]<sup>+</sup>, but the charge–charge interaction should have a dominant effect. The anion interaction with the probe is less specific. All IL anions are single-charged but can show remarkable differences in shape and charge distribution. Small and linear ions, like dicyanamide, can approach closer to the positive charge of Reichardt's dye and specifically interact with it. For large spherical anions like BF<sub>4</sub><sup>-</sup> and PF<sub>6</sub><sup>-</sup>, steric hindrance results in a less close interaction. This reduces the strength of the specific coulomb interaction according to inverse distance law. Specific short-range anion–probe interactions can be eliminated completely by removing all the specific effects of the chemical moieties of the anion. On the other hand, molecular solvents tend to align or anti-align their dipoles toward the positively- or negatively-charged centers, but the interactions are weaker and always due to the same species. These considerations are pictorially illustrated in Fig. 1.



**Fig. 1** The cation can get closer to the negative charge of Reichardt's dye (here represented as an ellipse) than the anion to the (delocalized and buried) positive charge. Molecular solvents align their dipoles with the electric field, but it is always the same molecule that interacts with the two charged centers.

In conclusion, some intrinsic characteristics of ILs lead to a kind of interaction with solvatochromic probes that is slightly different to molecular solvents. The extension of scales, parameters and concepts designed for molecular solvents need to be deeply and critically evaluated before being generalized and applied to ILs. Improved solvatochromic dyes, which show UV/vis absorption maxima unaffected by the electrostatic interaction between the IL anion and Reichardt's dye, have recently been proposed by Spange *et al.*<sup>46</sup> Unfortunately, only a limited number of the ILs in Table 1 have had "improved" Kamlet–Taft parameters reported, and therefore it has not been possible to verify if they are able to better describe the reactivity and selectivity of the previously investigated Diels–Alder reactions than the conventional ones.

Finally, among the attempts to rationalize the solvent effects of ILs, it is necessary to mention recently published data on the intramolecular Diels–Alder (the reaction of (*E*)-1-phenyl-4-[2-(3-methyl-2-butenyloxy)benzylidene]-5-pyrazolone).<sup>47</sup> The kinetic results were interpreted in this case in terms of "microviscosity", a property which should be proportional to the bulk viscosity but, at the same time, be affected by the mutual interactions between the solvent and the solute molecules. Despite the different viscosity, the reactions carried out in [Tf<sub>2</sub>N]<sup>-</sup> and [BF<sub>4</sub>]<sup>-</sup>-based ILs were characterized by nearly identical rate constants. Thus, the possibility that the substrate experiences a higher friction or microviscosity in [Tf<sub>2</sub>N]<sup>-</sup>-based ILs, even though the viscosity of these media are much lower, was proposed by considering that the strength of the cation–anion interactions should decrease from [BF<sub>4</sub>]<sup>-</sup> to [Tf<sub>2</sub>N]<sup>-</sup> and, consequently, the presence of [Tf<sub>2</sub>N]<sup>-</sup> as a IL counteranion should result in a greater extent of interaction between the cation and the substrate.

The necessity to use microviscosity to explain the kinetic behavior of this process confirms the inability of macroscopic properties to describe the solvent power of ionic media<sup>48</sup> and evidences the high degree of complexity of these systems.

In this work, Kumar *et al.* also evidence the fundamental feature differentiating intramolecular and intermolecular processes, and therefore the different role that microviscosity can have in the two processes; whereas the intramolecular Diels–Alder reaction experiences friction with the solvent molecules in the course of the rotational diffusion of the reacting moieties, the bimolecular process can be visualized as a translational diffusion of the reactants to form an "encounter complex". The frictional forces experienced in the course of translational diffusion need not be the same as those for rotational diffusion, particularly for microheterogeneous reaction media like ILs.

## Theoretical calculations

Although multiparameter linear energy relationships have contributed to clarifying some of the aspects related to the use of the ionic solvents in Diels–Alder reactions, it is evident that this approach presents some limitations. In particular, strong intercorrelations between the empirical parameters, which render the elucidation of the precise role of each solute–solvent interaction term difficult, and the fact that the meaning of the solvatochromic parameters may be not exactly the same for molecular solvents and ILs contribute to increase the degree of approximation of this kind of analysis.

Theoretical calculations generally represent a valid alternative to obtaining a greater insight into the solvation effects of specific reactions. In 2007, Zhang *et al.* evidenced<sup>49</sup> through a quantum chemistry calculation at the AM1, HF/6.31G(d) level, considering exclusively reagents (cyclopentadiene and methacrolein) and dimethyl imidazolium cations, the ability of the IL to act as a Lewis acid center in Diels–Alder reactions by decreasing the energy barrier and increasing the asynchronicity of the process.

Simultaneously, Jorgensen *et al.* reported<sup>50</sup> a theoretical study on the impact of acidic and basic imidazolium-based chloroaluminates ([emim]Cl–AlCl<sub>3</sub>) upon the cyclopentadiene and methyl acrylate Diels–Alder reaction rate by using quantum

and molecular mechanics (QM/MM/MC) simulations. Starting from the fact that the ability of the IL to act as hydrogen bond donor (cation) is moderated by its hydrogen bond accepting ability (anion effect), solute–solvent interactions in acidic and basic liquid melts were analyzed at key stationary points along the reaction coordinate. The reaction rate was found to be greater in the acidic than basic melt due to the less-dominant anion–cation interaction in the acidic medium, which favors better coordination of the imidazolium cation at the carbonyl group. In particular, the rate enhancements observed in acidic [emim]Cl–AlCl<sub>3</sub> systems were attributed to the preferential hydrogen bonding of the dienophile with the more sterically exposed C4 and C5 hydrogens on the imidazolium cation rather than the hydrogen on C2.

It is, however, noteworthy that if this mechanism is the sole one affecting the reactivity and selectivity, since the enhancement observed in *endo* selectivity and reaction rate in acidic [emim]Cl–AlCl<sub>3</sub> is significantly higher than that reported in any other IL, it is necessary to conclude that the coordinating ability of the anion(s) present in the acidic melt (AlCl<sub>4</sub><sup>-</sup> and Al<sub>2</sub>Cl<sub>7</sub><sup>-</sup>) is much lower than that characterising any other used anion!

Actually, acidic chloroaluminate ILs could also affect the Diels–Alder reaction through the direct interaction of the IL anion (Al<sub>2</sub>Cl<sub>7</sub><sup>-</sup>) with the carbonyl of the dienophile. It is indeed known that tetrachlorobenzoquinone (chloranil) exists in acidic melts (> 50% AlCl<sub>3</sub>) as a Lewis acid adduct with AlCl<sub>3</sub> (or Al<sub>2</sub>Cl<sub>7</sub><sup>-</sup>), coordinated at one of the carbonyl oxygens and at the C=C double bond, whereas no evidence for adduct formation was observed in basic melts (< 50% AlCl<sub>3</sub>).<sup>51</sup>

Finally, recently, the reaction of cyclopentadiene with methyl acrylate, acrolein and acrylonitrile in three ILs ([Hbim][Tf<sub>2</sub>N], [bmim][Tf<sub>2</sub>N] and [bm<sub>2</sub>im][Tf<sub>2</sub>N]) was investigated by some of our group at the DFT level.<sup>52</sup> Since the three ILs presented the same anion ([Tf<sub>2</sub>N]<sup>-</sup>), which, moreover, has been shown to be unable to give strong cation–anion interactions,<sup>53</sup> for reasons of computational cost, only one cation instead of a larger set of solvent ions was considered.

The main results of this investigation evidenced that the Diels–Alder reaction in the presence of the imidazolium cation proceeds *via* a concerted mechanism similar to the “uncatalyzed” cycloaddition, although the asynchronicity of the process is increased by the presence of the imidazolium cations.

The energetic differences between the reagents and the TSs for the *endo* and *exo* approaches, calculated for the three dienophiles in the presence of the above mentioned cations, were qualitatively in agreement with the experimental data and confirmed the high selectivity in favor of the *endo* path for the reaction of cyclopentadiene with acrolein or methyl acrylate in a [Hbim]<sup>+</sup>-based IL. On the other hand, structural data confirmed that the dienophile was coordinated to the most acidic hydrogen of the imidazolium ring, corresponding to the hydrogen atom on the nitrogen, when it is present. For the reaction of acrylonitrile in [bm<sub>2</sub>im]<sup>+</sup>, the dienophile appeared to be coordinated to the three hydrogen atoms of the methyl group at C2. However, going from [Hbim]<sup>+</sup> to [bm<sub>2</sub>im]<sup>+</sup> increased the distance between the cation and the dienophile. The effect of cation–dienophile coordination was stronger in the case of the *endo* arrangement, particularly in the reactions of acrolein and methyl acrylate in

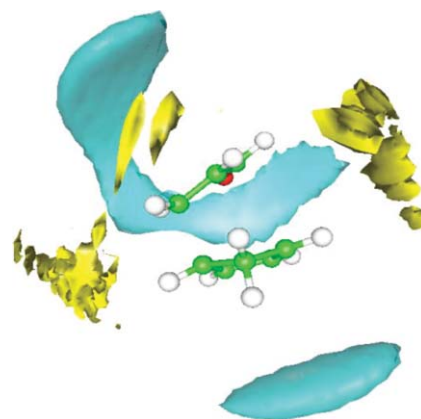
[Hbim]<sup>+</sup>, whereas the *exo* pathway was characterized by a lower cation sensitivity.

On the basis of these data, considering the interactions between cations and anions and the ability of ILs to give three-dimensional networks, it was hypothesized that the interaction between the IL cation and the dienophile may be affected by the whole ionic system, and the expression “clamp-effect” was used to define this interaction. More in detail, the IL cation interacts with the dienophile acting as a “clamp”, since in an IL, the freedom of motion of the cation is strongly limited by Coulombic interactions with the solvent bulk, which can be considered the clamp support. The nature of anion–cation interactions affects the ability of the IL to act as a support. However, the strength of the clamp effect is also determined by the cation and dienophile structure; the polarity of the substituent(s) on the double bond (CHO, COOCH<sub>3</sub>, CN) determines the strength of the interaction of the dienophile with the cation, which is also affected by the number and nature of available hydrogens on the cation. Electrostatic and steric effects therefore determine the nature of the interaction.

What are the consequences of cation–dienophile interaction and of the clamp effect on Diels–Alder reactions though? The interaction with the cation determines the polarization of the double bond of the dienophile, increasing its reactivity, whereas the clamp effect blocks one of the reagents, increasing the probability of efficient stacking in the TS.

However, the model used in this case was also an oversimplification of the real IL environment.

Therefore, to improve the description of ionic media, we have examined the Diels–Alder reaction of acrolein with cyclopentadiene in 1,3-dimethylimidazolium hexafluorophosphate using the KS-DFT/3D-RISM-KH method (Fig. 2).<sup>54</sup> In this formulation, the RISM method (which allows for a rapid evaluation of the solvent distribution function in the space around the solute and of the free energy of solvation) is coupled to a quantum mechanical DFT calculation through a self-consistent procedure. With this method, it is then possible to obtain reliable quantum mechanical calculations on molecules in the solvent with limited computational effort. On the basis of the 3D distribution functions of the anion and cation around the TS, it was possible to establish that the interaction between cation



**Fig. 2** The TS in [mmim][PF<sub>6</sub>]. Depicted are the probability distribution of the cation (cyan) and anion (yellow) around the TS, as obtained from KS-DFT/3D-RISM-KH.



and the TS is driven by oxygen–hydrogen coupling, although stacking interactions between the TS and the cation can be detected. The first solvation shell of the TS may be described by three cations (one coordinated with the carbonyl and two stacked above and below the TS) and three anions.

It is, however, noteworthy that, at least for the employed cation, the calculations suggest that the interaction of the carbonyl oxygen is stronger with the methyl groups and the hydrogens at C4 and C5 than with the hydrogen at C2, in agreement with the precedent finding by Jorgensen *et al.*, suggesting that the hydrogen at C2 is not fundamental.

The presence of the IL changes the geometry of the TS for all four pathways considered, deforming the diene–dienophile stacking geometry and enhancing the asynchronicity of the reaction when performed in these solvents.

Before examining in detail the solvation aspects, it is necessary to recall that the insertion of a solute in a solvent is characterized by a free energy of solvation that can be approximately divided in two parts: the change in electronic energy of the solute given by electrostatic and dispersion interactions with the solvent, and the change of solvent energy due to the necessary reorganization of the solvent molecules in order to embed the solute.

The most important solvent effect on the reaction rate emerging from these calculations is given by the solvation free energy, which promotes the aggregation of non-ionic compounds. This “solvophobic” effect, which can be considered similar to that of water, arises from the fact that the (generally positive) solvation free energy of a neutral solute in an IL is dominated by the unfavorable process of creating a cavity of suitable size to accommodate the solute. This process in ILs requires a considerable amount of work due to the lowering of the Coulombic interactions, which cannot be recovered by dipole–ion (or even less efficient) interactions. This effect is probably affected by the anion’s nature!

On the other hand, the *endo* selectivity enhancement appears to be driven by electronic energy; ILs enhance the  $\pi$ – $\pi$  dispersion interaction between reactants, probably by blocking the dienophile and consequently the diene. The previously hypothesized clamp-effect may find stronger support here.

The RISM approach has also been used to investigate the origin of the relatively moderate solvation effects of ILs with respect to water in determining the *endo/exo* selectivity; with the exception of acid chloroaluminates, selectivities in ILs are generally lower than in water. The Diels–Alder reaction of cyclopentadiene with methyl acrylate in 1,3-dimethylimidazolium chloride has been examined by Sato *et al.* by combining quantum molecular orbital theory with a 1D-RISM model that had been previously (and successfully) been used to explain the rate enhancement of Diels–Alder reaction rates in water.<sup>55</sup> Comparing the results related to the same reaction in three solvents ([mmim]Cl, water and dimethyl ether), the authors attributed the weaker solvation ability of the IL to the lower number density of this medium, giving rise to a lower electron density around the TS and thus to a reduced solvent–solute electrostatic interaction; this latter feature being strictly related to the bulkiness of the imidazolium cation. From this first section, one would think that the reduced selectivity is thus given by the reduction in the electronic reorganization contribution in ILs.

Consequently, in this paper, the authors focused mainly on electrostatic solute–solvent interactions, nevertheless correctly reminding us that solvophobic effects could (as effectively happens) play a major role.

Turning our attention to numerical data, it actually appears that in water the leading contribution to *endo/exo* selectivity is not the electronic reorganization energy but the solvation excess free energy; while in water, the selectivity is given by a noticeable (–2.97 kcal mol<sup>–1</sup>) difference in the excess chemical potential of solvation, in RTILs this difference is almost zero.

This aspect is given by the fact that, as already explained, in ILs, the solvation free energy receives the largest contribution by the necessity for cavity creation, which is a function of the dimensions of the TS rather than of its isomerization state, and is then poorly sensitive to a change in the *endo/exo* isomerization.

## Conclusions

In conclusion, kinetic and stereochemical studies on Diels–Alder reactions in ILs have shown that solvent and dienophile structure determine the reaction rate and selectivity, affecting the possibility of interactions between specific groups on the dienophile and IL components. Both the LSER approach and theoretical calculations show the primary role of the cationic component of the IL on the selectivity attributed, respectively, to the hydrogen bond ability ( $\alpha$ ) and the dipolarity/polarizability ( $\pi^*$ ) of a single IL cation, or to a more coordinated effect of the solvation shell. The first solvation shell, which may be described by three cations (one of which coordinated with the carbonyl group, and two stacked above and below the TS) and three anions, enhances the  $\pi$ – $\pi$  dispersion interaction between the reactants, probably blocking the dienophile and consequently the diene as a molecular clamp.

On the other hand, the effect of ILs on reactivity, which is described in a less efficient way by the LSER approach, is rationalized by theoretical calculations on the basis of a solvophobic effect, which arises from the fact that the solvation free energy of a neutral solute in an IL is dominated by the unfavorable process of creating a cavity of suitable size to accommodate it. This latter process is determined by the interactions between the IL components, so it is also affected by the anion’s nature.

The specific interactions of single IL constituents (anions and cations), considered, however, as *a part of a larger network and not as single species*, are therefore the fundamental factors affecting the reactivity and selectivity of Diels–Alder reactions.

## Acknowledgements

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