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Solvent Effect on a Model of S_NAr Reaction in Conventional and Non-Conventional Solvents

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Abstract

In this chapter some theoretical and experimental reports in order to elucidate solvent effects (preferential solvation and iso-solvation effects, respectively) over nucleophilic aromatic substitution reactions as reaction model were examined. Solvent effects phenomena are introduced to predict their mechanism highlighting the hydrogen bond role mainly in ionic liquids, a new generation of solvents that can be designed in order to improve the reactivities of the reacting pair and intermediate species through of the potential energy surface (PES). Then, the preferential solvent effect may be defined as the difference between local and bulk compositions of the solute with respect to the various components of the solvent; usually mixtures of solvents and iso-solvation effect indicate the composition of a mixture in which the probe under consideration is solvated by approximately an equal number of cosolvent molecules in the solvent mixture.

Keywords: solvent effects, preferential solvation, S_NAr reaction, ionic liquids, iso-solvation effect

1. Introduction

Studies suggest that nucleophilic aromatic substitution (S_NAr) reactions are significantly affected by the reaction media, because it involves the stabilization of species associated to the potential energy surface (PES) determining selectivity, reaction rates, and mechanisms [1–3]. In this chapter an integrative analysis based on experimental and theoretical results as an input to perform a deeper analysis based on preferential solvation and iso-solvation effects, respectively, is described. This chapter is organized by summarizing the main achievements on solvent effects based on S_NAr reactions considering that these reactions have widely been studied in water, conventional organic solvents (COS), and more recently in ionic liquids (IL) and mixtures of them [1–11]. Note that the most discussed articles are based on kinetic responses in order to evaluate the solvent effect over this reaction which has been used as model.

2. Nucleophilic aromatic substitution reactions

Nucleophilic substitution is an addition-elimination (A_ND_N) process that depending on the nature of the substrate, the attacking nucleophile, and the solvent

effect may lead to a nucleophilic substitution (NS) product or a S_NAr product or both [12–16]. A S_NAr reaction occurs in activated aromatic compounds bearing good leaving groups (LG). In general, it is widely accepted that the mechanism of the S_NAr reactions involves the formation of a σ -complex (also called Meisenheimer complex (MC)) that occurs after the nucleophilic attack step at the ipso atom of aromatic moiety. Next, the departure of LG with re-aromatization of the aromatic ring closes the set of steps to give the desired product. Commonly, the LG departure step is faster than the nucleophilic attack; therefore, the addition of the nucleophile to the ring moiety appears as the rate-limiting step in these processes [13, 17–24]. In the last time, a concerted reaction mechanism could be prevailing [25–27]. A lot of work has been carried out to clarify whether the concerted mechanism is an exception or the dominant pathway in these processes [28, 29].

2.1 Hydrogen Bond in S_NAr Reactions

Bernasconi et al. [23, 30] postulated the existence of an intramolecular hydrogen bond between a hydrogen atom of the nucleophilic center in the nucleophile and the ortho- NO_2 group of the substrate in order to explain the reactivity trends in ortho-halonitrobenzenes to respect para-halonitrobenzenes toward amines. Ormazábal-Toledo et al. [31] carried out computational studies about the role of HB effects along the intrinsic reaction coordinate profile, demonstrating that it promotes the activation of both the substrate and nucleophile, respectively. Note that the analysis was performed in transition state (TS) structures, because the reactant states hide most of the information about specific interactions that characterize the S_NAr reactions. Recently, Gallardo-Fuentes and Calfumán et al., respectively, showed that the HB not only determines the reactivities, but also it could be involved in concerted routes in S_NAr reactions [1, 26, 32].

3. Room temperature ionic liquids

Ionic liquids or room temperature ionic liquids (RTILs) are defined as molten salts (composed entirely of cations and anions) that melt below $100^\circ C$ [33] with remarkable physicochemical properties: non-flammable, non-corrosive, nonvolatile, and bulk physical constant, which can be tuned by the combination of different cations and anions [34–38]. RTILs are composed by bulky organic cations usually imidazolium or pyridinium derivatives substituted with alkyl chains and an inorganic or organic anion (usually a halide, tetrafluoroborate, hexafluorophosphate, and others). The high combinatorial flexibility has converted these materials into “designer solvents” or “task-specific” solvents [33, 35, 38] whose properties can be specified to suit the requirements of a particular reaction [2, 4, 12, 39]. For these reasons, RTILs have gained importance in the solvent effects field being recognized as very promising reaction media with green features.

3.1 S_NAr reactions in ionic liquids

A series of reaction have been studied in RTILs and mixtures of them with water or COS. The criteria to select the RTILs were based on the following: (i) the solubility of substrates and nucleophiles; (ii) to have a reasonable number of anions and cations to assess anion and cation effects; and (iii) to ensure that these RTILs do not interfere with the reaction [12]. Solvent effects in RTILs are a complex problem, because the solute-solvent interactions will be masked by the leading solvent-solvent interactions that are coulombic in nature. Some strategies to study

solvent effects in RTILs consider a reasonable large number of these and to evaluate their performance by fixing the anion and varying the cation and vice versa. For instance, a complete study based on the reaction of DNBSCl with piperidine was performed in 17 RTILs considering water as a solvent reference. This study identified three groups of RTILs showing 1-ethyl-3-methylimidazolium dicyanamide (EMIMDCN) as the best solvent considering all the studied RTILs and 21 COS [12, 40]. EMIMDCN shows a catalytic behavior attributed to its high polarizability given by the dicyanamide anion (DCN⁻), which presents a highly rich π electron density, and its size could be in relationship with steric hindrance effects. Note that ethylammonium nitrate (EAN) was the only protic RTIL that decreased the reaction time in comparison to water and EMIMDCN, respectively. Then, a comparative study of the reaction of DNBSCl and propylamine in COS and RTILs, respectively, was performed in order to analyze the nature of the nucleophile. Piperidine showed to be more active than propylamine in polar solvents with the ability to donate and accept HB, while the reaction of propylamine was favored only with solvent that can accept HB, being the best COS solvent: N,N-dimethylformamide (DMF). Note that, in all the studied RTILs for propylamine, the reactivities of the reactions were lower than piperidine. This response was attributed to the capacity of the RTILs to donate/accept HB in agreement with the COS behavior [12]. On the other hand, propylammonium nitrate (PAN) was able to emulate the HB behavior of water toward the reaction between 4-chloroquinazoline and aniline [39]. PAN could be donating an HB by the ammonium moiety of PAN toward the substrate emulating an electrophilic solvation suggested in aqueous media improving its reactivity toward the nucleophile. These results are in agreement with the report of Welton et al. [2] based on the task-specific design of RTILs in order to optimize those properties that enhanced the reaction reactivities. Harper et al. reported the main role of the RTIL structure on the reaction rates of S_NAr reactions [41, 42].

3.2 Binary mixtures based on ionic liquids

The use of RTILs or ionic liquid binary mixtures could give variations in the structure of the ionic lattice of neat ILs after mixing [43–45]. This fact may have significant repercussions on the nature and strength of the interactions that contribute mainly to coulomb interactions that determine the 3D structure of ILs [46, 47]. Studies of binary mixtures with common anions, for instance, the same cation but different anions, have shown how the presence of random co-networks or block co-networks depends on the size of the anions [4, 47, 48]. Seddon suggests the use of IL mixtures to expand the range of room temperatures in ILs [49]. Initially, the hygroscopic nature of the ILs was a problem; however the high capacity of the ILs to solubilize water opens a wide spectrum of reaction media, mainly based on the role of the hydrogen bond (HB) and electrostatic interactions between molecules in the mixture. Reports have shown that the addition of COS to ILs may affect significantly the density, viscosity, and conductivity with respect to pure ILs. For instance, the direct relationships between the viscosity of the IL/COS mixtures with the solvent dielectric constant (ϵ) of the COS pure [50, 51]. It may be attributed to the difference in the ion-dipole interactions between the ions and solvents. The addition of water to ILs may change the molecular structure of pure ILs probably due to HB between the water molecules and the anions of the ILs [52, 53]. Sanchez et al. studied solvent mixtures between 1-butyl-3-methyl imidazolium tetrafluoroborate (BMIMBF₄)/water at different molar fractions, observing on the studied range of compositions, a border line located close to $\chi = 0.2$. Before this value indicates that the added RTIL promotes the reactivity of the substrate by preferential solvation. After this value, the rate coefficients remain approximately constant. At low concentrations the water begins to break down the 3D

structure of the ILs, which then goes on to form ionic clusters as the concentration of water increases until eventually ion pairs form, which are the dominant species in the aqueous solution [10, 46, 48].

4. Interactions and solvent effects

It is well known that the chemical reactivity is determined by the ability of the solvent to interact with solute, intermediates, and transition state (TS) structures along the reaction pathway [1–3]. The main difference between COS and RTILs are the electrostatic solvent-solvent interactions between cation-anion and cation-cation interactions [33]. These interactions in the COS are moderate dipole-dipole interactions; in the RTILs they become the leading term (ion-ion interactions) that are expected to outweigh the target solute-solvent interactions. Solute-solvent interactions contain the relevant information about catalysis, stabilizing/destabilizing effects affecting the electrophile/nucleophile pair (solute), TS structures, and the intermediate in a polar process [1]. Solvent effects can be split into two types: non-specific interactions and specific interactions, including all the possible interactions that can occur between solvent and the electrophile/nucleophile pair [5, 52].

4.1 Preferential solvation

Solvent effects can be split into two types: non-specific and specific interactions, including all the possible interactions that can occur between the solvent and solute [5, 39, 54]. Then, preferential solvent may be defined as the difference between local and bulk composition of the solute with respect to the various components of the solvent, usually mixtures of solvents [5, 55–57]. The “bulk of the solvent” is treated as the external shell, and it can be described using the classic theories of Kirkwood-Onsager, models of solvation based on reaction field theory or molecular dynamic [55, 58, 59]. Then, in a binary mixture of protic solvents, the “preferential solvation” may be cast into the form of specific solute-solvent interactions described as local solvation, which may be defined as a “first solvation shell.” The local solvation may be classified as electrophilic or nucleophilic, respectively [17, 60–63]. Electrophilicity and nucleophilicity concepts are related to electron-deficient (electrophile) and electron-rich (nucleophile) species [39, 64, 65]. These concepts are based on the valence electron theory of Lewis [66] and the general acid–base theory of Brønsted and Lowry [67, 68] and introduced by Ingold in 1934. Then, for a mixture of polar solvents, the “electrophilic solvation” represents the specific interaction through a HB with the hydrogen atom of the solvent, whereas “nucleophilic solvation” describes a specific interaction through a HB between an acidic hydrogen atom of the solute and the heteroatom of the solvent [5, 60–63]. Mancini et al. have reported preferential solvation of 1-halo-2,4-dinitrobenzenes with amines in mixtures of dichloromethane with polar protic/polar aprotic solvents [7, 44, 45, 69, 70]. Ormazabal-Toledo et al. [5] reported an integrated experimental and theoretical study of 2,4,6-trinitrophenyl ether with a series of secondary alicyclic (SA) amines in ethanol/water mixtures at different compositions. In it only piperidine was sensitive to preferential solvation at high proportion of water. Piperidine increases its rate coefficient values suggesting a stabilization of the MC by HB displayed by the presence of more water molecules in the first shell at these proportions of water in the studied mixtures. This result shows that the environment of the MC changes for different solvent compositions. Then, for the remaining amines the environment showed to be similar being it attributed to polar nature of the substituent at position 4, suggesting that their kinetic responses are independent of the bulk properties of the reaction media. On

the other hand, Alarcón-Espósito et al. [1] studied the reaction between 1-chloro and 1-fluoro-2,4-dinitrobenzenes, respectively (CIDNB and FDNB, respectively) with morpholine (a SA amine) in acetonitrile (MeCN)/water mixtures at different compositions. Experimental results were complemented with a theoretical analysis in order to study the bulk and specific interactions of solute-solvent in mixtures of a COS (MeCN) and water. Note that both solvents display significant HB abilities. Then, in 90% vol. MeCN substrates both displayed the maximum value of the rate coefficient constants. On the other hand, the exploration of the PES using the “super-molecule method” revealed that the solvation of the TS structure associated to the rate determining step (RDS) of the reaction mechanism expressed in the mode water/MeCN outweighs over MeCN/water, suggesting a preferential solvation in favor of the aqueous phase. The super-molecule model introduces solvent molecules explicitly around the solute. This model provides a detailed synopsis of the field of solvation sufficient to describe the interactions between the solute and solvent [71].

4.2 Iso-solvation

The concept of iso-solvation has been introduced to indicate the composition of a mixture in which the probe under consideration is solvated by an approximately an equal number of cosolvent molecules in the solvent mixture [48]. This effect has been extensively observed in COS mixtures [72–74]. Alarcón-Espósito et al. [48] studied the reaction between CIDNB with morpholine in a series of mixtures of ILs involving imidazolium cations. Iso-solvation effects were observed in the following mixtures: 1-ethyl-3-methyl imidazolium thiocyanate/1-ethyl-3-methyl imidazolium dicyanamide (EMIMSCN/EMIMDCN), 1-butyl-3-methyl imidazolium dicyanamide/1-butyl-3-methyl imidazolium tetrafluoroborate (BMIMDCN/BMIMBF₄), BMIMBF₄/1-butyl-3-methyl imidazolium hexafluorophosphate (BMIMPF₆), and BMIMPF₆/1-butyl-3-methyl imidazolium tris(pentafluoroethyl) trifluorophosphate (BMIMFAP), respectively. Iso-solvation regimes correspond to a solvent composition regime where the solute is being solvated by approximately the same number of different solvent molecules in the mixture. These results showed that for significant changes in composition, the rate coefficients remain approximately constant. On the other hand, for the solvent mixture BMIMBF₄/BMIMPF₆ at 0.9 molar fraction of BMIMBF₄, a slightly better kinetic response is observed than the pure BMIMBF₄ and BMIMPF₆. Another interesting result was observed in the mixture of EMIMSCN/EMIMDCN; an increasing proportion of EMIMSCN with respect to EMINDCN results in a decrease of the rate coefficient within the range 0.1–0.75 in molar fraction of EMIMSCN. This result could be expressed as a competition between the anions toward the reaction center driven by the basicity of the reaction media.

4.3 Polarity and solvent effects

Experimentally, the most common way to measure the polarity of a solvent is through its (bulk) dielectric constant (ϵ). The concept of polarity has been defined as the sum of all possible intermolecular interactions between the solvent and the solute, including specific interactions, for instance, HB effects, dipole-dipole, dipole-induced dipole, electron pair acceptor-electron pair donor, and acid-base interactions [1, 33]. Gazitúa et al. [12, 40] studied the solvation patterns of 21 COS and water over the reaction between 2,4-dinitrophenylsulfonyl chloride (DNBSCI) with SA amines in order to determine the solvent polarity effect on the reaction mechanism. Note that solvent polarity became relevant only in the reactions that proceeded by the non-catalyzed route. On this way, water and tetrahydrofuran

(THF) have a key role due to its amphiphilic character as an HB donor/acceptor that promotes a nucleophilic activation at the nitrogen center of the piperidine (nucleophile).

5. Solvent models

5.1 Kamlet-Taft model

Solvent effect studies have been focused mainly on the polarity of the reaction medium as a determinant of chemical reactivity properties. Experimentally, the most common way to measure the polarity of a solvent is through the ϵ . However, the measure requires that the reaction medium will be non-conductive, which does not happen in the RTILs. The concept of polarity has been defined as the sum of all possible intermolecular interactions between the solvent and a solute, excluding those interactions that lead toward chemical reactions of the solute and including Coulombic interactions, HB interactions, dipole-dipole, dipole-induced dipole, electron pair acceptor-electron pair donor, and acid-base interactions [1, 33]. There are many empirical solvent polarity scales [75–83] that attempt to give quantitative estimates of solvent polarity, some of those were applied to RTILs [84]. However, the high number of interactions in non-conventional reaction media cannot be incorporated in a measurement or polarity scale. The most used solvent polarity scale is the one developed by Kamlet and Taft [78] based on solvatochromism properties that show specific and non-specific interactions. Solvatochromism is solvent dependence of the electronic spectrum of chromophore. Intensity, position, and shape of absorption bands of dissolved chromophores are influenced by the change in solvents or mixture of solvents, according to their electronic and molecular structure, due to the different stabilization of their electronic ground and excited states. Therefore, any solvent-dependent property (SDP) in solution is normally expressed as a linear solvation free energy relationship (LSER) as follows:

$$SDP = SDP_0 + a \alpha_s + b \beta_s + s \pi_s^* \quad (1)$$

where SDP corresponds to any kinetic property, namely, selectivity or reaction rate coefficients, which is modeled as a linear combination of two H-bond terms, one for hydrogen bond donor ($a \alpha_s$) and hydrogen-bond acceptor ($b \beta_s$) and a dipolarity/polarizability term ($s \pi_s^*$), with SDP_0 a constant describing intrinsic properties of the solute [84]. In this approach, empirical solvatochromic parameters are introduced to describe specific HB interaction, ion-dipole, dipole-dipole, dipole-induced dipole, solvophobic, dispersion London, and possible π - π and p - π stacking effects. The reason is that while empirical solvatochromic parameters in COS work reasonably well, for RTILs they consistently fail. The main reason seems to be the transferability of the response of a particular probe chromophore from some known SOC to RTILs. This transferability would warrant that the polarities of the RTILs and the SOC are the same and that the appropriate value of the parameter can then safely be assigned to the RTIL. The second implicit assumption is that the effect of transferring from a SOC to an RTIL is the same for all probes. They conclude that it is important to consider the nature of the chromophore as well as the solvent when establishing reliable solvent polarity parameters, mainly when this chromophore is transferred from a neutral molecular solvent to an RTIL. The main message, however, is that it cannot be a priori established if one solvent polarity scale with respect to another one is right or wrong: “each scale will turn useful in a given set of circumstances and in other ones they will not” [1, 12].

5.2 Theoretical models of solvation

In pure conventional solvents, the determination of properties and type of interactions has been reasonably achieved with the use of non-specific solute-solvent interactions, based on continuum dielectric models [85, 86]. In RTILs, the results are both scarce and not yet systematized [87, 88]. The super-molecule model provides a detailed synopsis of the field of solvation [71].

5.3 Gutmann's donor and acceptor numbers

Donor (DN) and acceptor (AN) numbers proposed by Gutmann [89–91] are used to describe acid-base solvent properties in RTILs based on a reformulation by Schmeisser et al. [92, 93]. On the original definition of Gutmann, DN and AN are a quantitative measure of Lewis basicity and acidity of a solvent, generally a nonaqueous media [4, 91]. These numbers can be measured by calorimetric technique and by using the chemical shift in ³¹P NMR spectra [92, 94]. In COS these parameters are used in order to describe the ability of solvents to donate or accept electron pairs or at least electron density to the substrate. Then, DN represents a measure for the donor properties of a solvents, and AN is a measure of the electrophilic properties of a solvent. DN parameter in RTILs shows a strong dependence on the anionic component of the RTIL; however, AN is dependent on both anionic and cationic moieties of the RTIL [92].

Alarcón-Espósito et al. [4] studied three families of RTILs, based on 1-ethyl-3-methyl imidazolium (EMIM⁺), 1-butyl-3-methyl imidazolium (BMIM⁺), and 1-butyl-1-methyl-pyrrolidinium (BMPyr⁺) cations, respectively, with a wide series of anions in order to evaluate both models of solvent effects toward the reaction between 1-chloro-2,4-dinitrobenzene with morpholine by kinetic experiments. The first approximation of solvent effects was attributed to an “anion effect.” This effect appears to be related to the anion size, polarizability, and its HB ability toward the substrate. The comparison between rate constants and Kamlet-Taft solvatochromic model systematically failed. However, the anion effect was confirmed by performing a comparison of the rate constants and DN emphasizing the main role of the charge transfer from the anion to the substrate.

6. Conclusions

In this chapter some theoretical and experimental reports in order to elucidate solvent effects over nucleophilic aromatic substitution reactions were examined. Solvent effects are introduced over mechanistic behaviors highlighting the HB role mainly in RTILs, a new generation of solvents that can be designed in order to improve the reactivities of the reacting pair and intermediate species through the PES. For instance, (i) solvent polarity could be modulating the reaction pathways differently; (ii) the ability of the solvent to establish HB could drive the reaction mechanism opening the possibility of preferential solvation; (iii) in mixtures of solvents and depending on the constituents of them could be affecting the reaction rate by solvent structural organization, viscosity, and HB interactions; and (iv) in ionic liquids the solvent effect could be attributed to an anion effect being it related to the size and HB abilities of the anions.

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