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Two-dimensional ultrafast vibrational spectroscopy of azides in ionic liquids reveals solute-specific solvation

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The stereochemistry and the reaction rates of bimolecular nucleophilic substitution reactions involving azides in ionic liquids are governed by solute-solvent interactions. Two-dimensional ultrafast vibrational spectroscopy (2D-IR) shows that the picosecond dynamics of inorganic azides are substantially slower than organic azides in a series of homologous imidazolium ionic liquids. In water, both organic and inorganic azides spectrally diffuse with a ~2 ps time constant. In the aprotic solvent tetrahydrofuran, both kinds of azides spectrally diffuse on a timescale > 5ps. In ionic liquids like 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF₄]), organic azides spectrally diffuse with a 2–4 ps time constant, and inorganic azides spectrally diffuse with a > 40 ps time constant. Such a striking difference suggests that neutral (organic) and charged (inorganic) azides are incorporated in the ionic liquids with different solvation structures.

The rate constants of bimolecular nucleophilic substitution (S_N2) reactions involving azides can vary as much as three orders of magnitude depending on the polarity of the solvent.¹ Ionic liquids are unique polar reaction media for S_N2 reactions which provide definite advantages in rates, specificity, and yield.^{2–4} Unlike molecular solvents, ionic liquids are room temperature molten salts, composed entirely of cations and anions. How such complex solvent media solvate reagents and thus affect reaction outcomes remains unclear.^{5,6,7} In this work, we test the hypothesis that azides in ionic liquids segregate to different local solvent environments based on their charges or functional groups. To study the differential local environment of these important reagents, we use their azide asymmetric stretch as a probe to interrogate the local structure and dynamics of these fluids. In this report, we compare the picosecond dynamics of organic and inorganic azides in water, tetrahydrofuran (THF) and in ionic liquids through ultrafast two-dimensional vibrational spectroscopy (2D-IR). The organic azides in our study are large neutral molecules. In contrast, the investigated inorganic azide ions are small, charged species. Whereas the dynamics of

organic and inorganic azides are similar in water and THF, they are strikingly different in imidazolium-based ionic liquids, indicating different solvation structures. Such insights are important because microsolvation influences the reaction mechanism of a nucleophilic substitution reaction.⁸

Nucleophilic substitution reactions are the most studied class of reactions in ionic liquids. Previous work with azides as reagents in ionic liquids indicated that substitution reactions are preferred to elimination pathways even in the case of sterically hindered substrates.² The azide anion is suggested to be a better nucleophile in ionic liquids than in methanol.⁹ In general, reactions in ionic liquids appear to have intermediate rate between those in methanol and in dimethylformamide (DMF), and promote specific products.¹⁰ The solvent properties of ionic liquids have been related to macroscopic parameters like polarity and dielectric constant (parameters which have been extensively used for molecular solvents to predict rates and chemical mechanisms), but many molecular details are missing.^{11–14} Studies with dyes in ionic liquids showed that ionic liquids have the same or similar properties as polar solvents.¹⁵ However, these studies cannot explain why the same reactions in these fluids produce selective products with rates that are different from polar solvents. Many studies, both experimental^{7,16–18} and theoretical^{19,20} indicate that imidazolium-based ionic liquids are heterogeneous in nature with distinct polar and non polar regions. Thus, there is an immediate need to develop a better molecular-level solvation picture of these complex solvents. However, investigating solvation in liquids is a challenge because of the short length and time scales involved. The first solvation shell persists only for few picoseconds making it difficult to characterize the solute-solvent interactions with standard techniques.

Our approach to investigate solvation in ionic liquids takes advantage of the spectroscopic properties of azides. Azides are stable vibrational chromophores with a strong antisymmetric stretch absorption in the free spectral window between 2000 cm⁻¹–2200 cm⁻¹ (Fig. 1). In molecular solvents and proteins, the antisymmetric stretch of azides report structure and dynamics of the local environment.^{21–23} Our strategy is to use this vibrational mode to access the interactions of azides with the ionic liquid.

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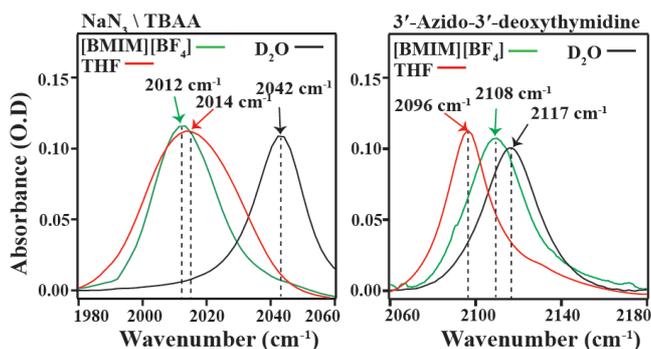


Figure 1. Representative FTIR of an inorganic and an organic azide shows that both compounds red shift on changing the solvent from D₂O to [BMIM][BF₄]/THF, although the magnitude of the red shift is larger for the inorganic azide. TBAA : tetrabutylammonium azide

To study the differences between ionic liquids and typical molecular solvents at microscopic level, we compare a series of organic azides (2-azido ethanol, 3-azido propylamine, and 3'-azido-3'-deoxythymidine) with inorganic azides (sodium azide (NaN₃) and tetrabutylammonium azide) in a series of protic ionic liquids (1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF₄]), 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF₆]), 1-ethyl-3-methylimidazolium tetrafluoroborate, [EMIM][BF₄]), THF, and deuterated water (D₂O). These reagents were dissolved in ionic liquids under same conditions as suggested to carry wet chemical synthesis in this medium. The residual water in these ionic liquids was comparable across various solutions (Supplementary information Fig. S1). The water content is similar to that reported in literature to for S_N2 reactions.²

From the perspective of the linear vibrational spectra, these ionic

liquids behave like aprotic molecular solvents. The azide asymmetric stretch red-shifts ~10 cm⁻¹ upon going from water to [BMIM][BF₄] for organic azides and ~25 cm⁻¹ for inorganic azides (Fig.1, Supplementary Information S2). Similar red-shifts are observed for organic and inorganic azides compounds in aprotic molecular solvents like THF (Fig 1) or DMSO when compared to water, due to the special hydrogen bonding environment of water.^{24–28} The linewidths of both kinds of azides in D₂O and [BMIM][BF₄] are also similar.

To gain insight to the structure and dynamics of the azide solvation shell, we use 2D-IR spectroscopy, which can characterize the solvation dynamics of liquids on short timescales ranging from hundreds of femtoseconds (fs) to tens of picoseconds (ps). A 2D-IR spectrum is a 2D contour plot obtained by spreading the molecular response of a system, due to vibrational excitation, over two frequency axes at a defined time period called the waiting time, T. In essence, the 2D-IR spectrum is a frequency correlation map, showing the sampling of the local environment as a function of time by the probe molecules. To generate such a correlation map, a pair of pump pulses excites the azide vibration and a probe pulse interrogates the vibration after a waiting time, T. The ω₁ axis is the azide initial frequency whereas the ω₃ axis is the final azide frequency (Fig. 2, Top). When T is short, ω₁ and ω₃ frequencies are highly correlated and the spectra are stretched along the diagonal. As the local environment changes due to thermal motion, the azides forget their initial frequency, frequency correlation is lost, and the spectra become round.

The qualitative information based on line shape can be made quantitative. The center line slope (CLS) and 2D-ellipticity are approximately proportional to the frequency-frequency correlation function (FFCF),^{29,30} which is the link to the underlying microscopic

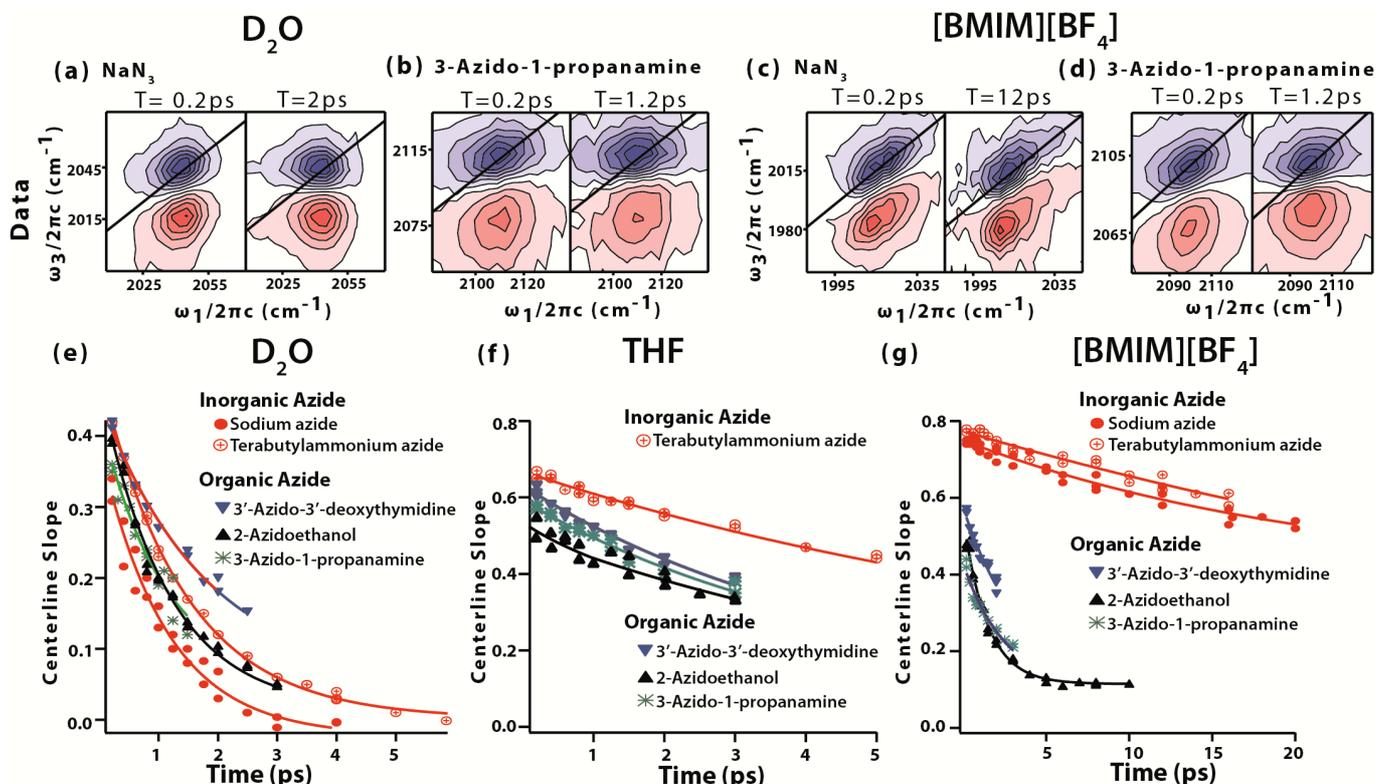


Figure 2. Top: 2D-IR spectra of an inorganic (a) and an organic azide (b) in D₂O shows similar changes in contour shapes within the waiting time of ~1.2 ps. In [BMIM][BF₄], 2D-IR spectra of the inorganic azide (c) shows substantially slower change in contour shape than the organic azide (d); Below: Centerline slope decays within 1-2 ps in D₂O (e) and greater than 5 ps in THF (f) for both kinds of azides. In [BMIM][BF₄] (f), the decay timescales for organic azides are within 5ps whereas for inorganic azides it is > 10 ps.

dynamics. From the decay of the FFCF, we can quantify the characteristic solvation timescale, τ .

In D₂O, 2D-IR spectra of both organic and inorganic azides show rapid loss of frequency correlation due to making and breaking hydrogen bonds. At $T = 0.2$ ps, the 2D-IR spectra are substantially elongated along the diagonal (Fig. 2a). At $T = 2$ ps, the spectra are no longer tilted. The CLS starts with an initial value of ~ 0.4 and decays to 0 within a few picoseconds (Fig. 2e). Fitting the CLS to a single exponential,

$$C(\tau) = A \exp[-(t/\tau)]$$

gives a ~ 2 ps time scale for all azides studied (Table 1). Analysis of the 2D-IR data by the ellipticity method also validates the observed trend (Supplemental Information). The picosecond timescales are consistent with the rates of hydrogen bond making and breaking in water as well as local electric field fluctuations.^{31,32} Thus, water is a uniform medium for organic and inorganic azides.

In the aprotic solvent THF, the spectral diffusion of both kinds of azides is slower than in water. The CLS of organic azides starts from a smaller value (~ 0.45) than the inorganic counterpart (~ 0.65), and both of them spectrally diffuse on timescales > 5 ps (Table 1). The dynamics observed for N_3^- are a factor of 1.5 – 2 slower than the organic azides. The mild slow down is likely caused by enhanced solvent structure in the first solvation shell around the solute due to electrostriction^{33,34}. Our results are in line with the dynamics of azides reported for other aprotic solvents like DMSO³⁵ or THF²³. Whether this trend is general to broader classes of aprotic solvents, however, has not been established. The dynamics of both kinds of azides may vary depending on the aprotic solvent, which will be explored in future work. With this complication in mind, THF is also a uniform medium for the organic and inorganic azides.

In [BMIM][BF₄], the 2D-IR spectra of organic and inorganic azides are markedly different. Whereas the organic azides (Fig. 2d) spectrally diffuse within 5 ps and become round, the inorganic azides (Fig. 2c) show high degree of correlation between the initial and the final frequencies even after >10 ps. The CLS for the organic azides starts at 0.6 and decays by $\sim 50\%$ within ~ 3 ps; the CLS for the inorganic azides starts at 0.8 and decays by only $\sim 20\%$ within the experimental time window (20 ps). The spectral diffusion of these inorganic azides persists for more than 20 ps (Table 1). Organic azides, on the other hand, spectrally diffuse on timescale < 5 ps.

Table 1. FFCF decays in D₂O, THF, [BMIM][BF₄] and [EMIM][BF₄]

Sample	D ₂ O	THF	BMIM BF ₄	EMIM BF ₄
	τ_{cls} (ps)	τ_{cls} (ps)	τ_{cls} (ps)	τ_{cls} (ps)
NaN ₃	1.1 ± 0.2	-	45 ± 7	-
TBAA	1.2 ± 0.4	9.2 ± 0.5	56 ± 12	19 ± 3
AZT	1.4 ± 0.1	4.8 ± 0.4	4.6 ± 0.4	3.3 ± 0.2
AE	1.0 ± 0.3	4.1 ± 0.5	3.9 ± 0.1	2.0 ± 0.1
AP	1.1 ± 0.1	6.1 ± 0.5	4.0 ± 0.3	2.9 ± 0.5

NaN₃: Sodium azide, TBAA: Tetrabutylammonium azide, AZT: 3'-azido-3'-deoxythymidine, AE: 2-azido ethanol, AP: 3-azido propylamine
Correlation decay times (τ_{cls}), as obtained from centerline slope method by fitting an exponentially decaying function, clearly show that the timescales of spectral fluctuations of azides is different in ionic liquids compared to D₂O.
*** See footnote³⁶

The same trends hold for [EMIM][BF₄] (Table 1). NaN₃ is only sparingly soluble, but tetrabutylammonium azide is soluble to 30

mM concentrations. The dynamics of tetrabutylammonium azide in [EMIM][BF₄] are faster than in [BMIM][BF₄], (19 ps vs 50 ps), but this is still substantially different than the dynamics of the organic azides (~ 2 ps) (Table 1). Similar trends are observed in [BMIM][PF₆] (Supporting Information Fig. S8). Thus, imidazolium-based ionic liquids are not uniform media for organic and inorganic azides.

Viscosity may cause differences in the dynamics of organic and inorganic azides in ionic liquids. Solvation dynamics, in the timescale of picoseconds or longer, are diffusive depending strongly on the viscosity of the ionic liquid. Dynamic Stokes shift, fluorescence up-conversion and optical Kerr gate measurements of many ionic liquids with dyes as probes have shown that the ultrafast solvation response could be separated into a subpicosecond inertial component and a much slower diffusive component.^{18,37} The time constant of the slower diffusive component was found to be correlated with the ionic liquid viscosity. In our studies, the viscosity of [EMIM][BF₄] (32-43 cP) is smaller compared to [BMIM][BF₄] (92-219 cP).^{38,39} As expected, all the reagents spectrally diffuse at a faster rate in [EMIM][BF₄] compared to [BMIM][BF₄]. However, the spectral diffusion of neutral molecules is still much faster than the charged ions, showing that viscosity alone is not responsible for the observed differences.

Long alkyl chain ionic liquids have well segregated polar and non-polar domains.^{19,20} [BMIM][BF₄] is a border-line case, with only a hint of the pre-peak in the x-ray scattering that indicates this phase segregation.⁴⁰ So, it is conceivable that the organic azides migrate to the non-polar domains whereas the charged inorganic azide anions station themselves in the polar domains. Our experiments with [EMIM][BF₄], however, rule out heterogeneity as the primary cause of the difference in dynamics. In [EMIM][BF₄], the alkyl chains are not long enough to form well-defined polar and non-polar domains, but differential solvation is still present.

Water may influence the dynamics of solutes in ionic liquids and, indeed, in aprotic solvents. The water content of our ionic liquids is between 300-600 ppm and comparable across various samples, so differences in water content is not the cause of the observed differences between organic and inorganic azides. Nevertheless, recent work in our laboratory with ionic liquids has demonstrated that water can change the dynamics of thiocyanate probes in complex ways when it is in the first solvation shell.⁴¹ What role water plays (if any) in the dynamical differences we see between the organic and inorganic azides will be explored in the future.

We hypothesize that different local structures exist around the N_3^- and organic azides. The smaller, harder N_3^- anions may interact directly with the most hydrogen-bond donating group of the imidazolium ring, the 2-position, and be directly incorporated into the ion network, which exists regardless of the length of the alkyl chains. The direct evidence of hydrogen bonding of N_3^- with the imidazolium cation is subtle in the linear infrared spectrum.²⁸ Nevertheless, molecular modeling⁴² has shown that small anions can effectively compete against larger anions; in our case N_3^- competes against [BF₄]⁻ or [PF₆]⁻. Additionally, this type of competition has been observed experimentally in other systems as well, for example our recent work with SCN⁻ as probe in a BMIM-based ionic liquids^{43,44} and Reichardt's dye in a wide variety of ionic liquids.¹⁰ It is therefore plausible that N_3^- competes for the 2-position of the imidazolium. In pure ionic liquid, this position is occupied by [BF₄]⁻. This scenario changes when the azide anion is introduced in

the ionic liquid. There is a competition for this site near the imidazolium cation leading to the incorporation of the azide anion in the charged network.^{45–47} The breaking and reforming of such ion complexes causes the slow dynamics that we observe. An alternative explanation could be based on the charge of the azide ions. Simulation with optical dyes has shown that translation of anions dominates the solvation response in ionic liquids. It is thus possible that the repulsion between the negative charge N_3^- and the solvent $[BF_4]^-$ anion causes the difference in solvation structure and dynamics when compared to neutral organic solutes.

Though we cannot definitively assign the solvation environment of the organic azides, we suspect that they are associated with the anion with the azide moiety and interact weakly with the imidazolium ring. Experiments^{10,48} and theory⁴⁹ have shown that small organic molecules with alcohol or having hydrogen donor capability (analogous to our 2-azidoethanol, 3'-azido-3'-deoxythymidine, and 3-azido-1-propanamine) are strongly hydrogen bonded to anions like BF_4^- or PF_6^- . Such association is possible due to large local fields near the fluorine atoms. Thus, our organic molecules are primarily anchored near the solvent anion through hydrogen bonding.

In conclusion, we have demonstrated that differential solvation dynamics exist in ionic liquids. Further assignment and characterization of these features in collaboration with molecular modelling is underway to offer an avenue to tune to reactivity of these synthetically useful moieties.

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