An Unusual Salt Effect in an Interfacial Nucleophilic Substitution Reaction

Shuheng Li and Milan Mrksich*

Departments of Chemistry and Biomedical Engineering, Northwestern University, Evanston, Illinois 60208, United States

ABSTRACT: This paper reports a kinetic characterization of the interfacial reaction of *N*-methylpyrrolidine with a self-assembled monolayer presenting an iodoalkyl group. SAMDI (self-assembled monolayers for matrix-assisted laser desorption/ionization) mass spectrometry was used to determine the extent of reaction for monolayers that were treated with a range of concentrations of the nucleophile for a range of times. These data revealed a second-order rate constant for the reaction that was approximately 100-fold greater than that for the analogous solution-phase reaction. However, addition of sodium iodide to the reaction mixture resulted in a 7-fold decrease in the reaction rate. Addition of bromide and chloride salts also gave slower rate constants for the reaction, but only at 100- and 1000-fold higher concentrations than was observed with iodide, respectively. The corresponding solution-phase reactions, by contrast, had rate constants that were unaffected by the concentration of halide salts. This work provides a well-characterized example illustrating the extent to which the kinetics and properties of an interfacial reaction can depart substantially from their better-understood solution-phase counterparts.
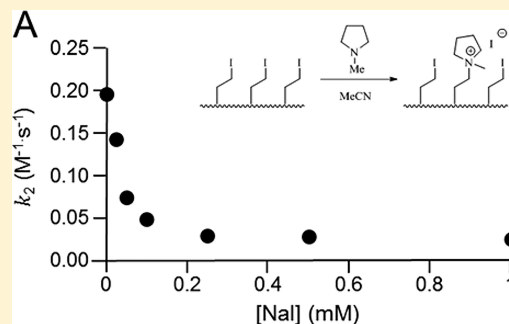
INTRODUCTION

Interfacial reactions of an immobilized molecule with a soluble reagent are important in a variety of contexts, including the preparation of biochip arrays,[1−6] the fabrication of photovoltaic devices,[7−9] and the preparation of catalytic materials.[10−12] Yet, in comparison to solution-phase reactions, the development of interfacial reactions remains challenging, primarily because it is difficult to characterize the products and yields for reactions that occur at a surface. In practice it is assumed that interfacial reactions proceed as their solution-phase counterparts do, even though a limited number of examples have shown that the unique microenvironments present at the interface can lead to dramatic differences in the kinetics and mechanisms of reactions.[13−22] In the present work, we characterize a nucleophilic substitution reaction of *N*-methylpyrrolidine with an iodo-terminated self-assembled monolayer and we show that the rate constant for this reaction is greater than expected based on the corresponding solution-phase reaction, and that it is unusually sensitive to the concentration of halide salts. This work provides a well-characterized example of the extent to which an interfacial reaction can differ from its solution counterpart and further presents self-assembled monolayers for matrix-assisted laser desorption/ionization (SAMDI) mass spectrometry as an enabling method for kinetic studies of a broad range of interfacial reactions.

Several reports illustrate the ways in which the interfacial microenvironment can alter the kinetics and products of common reactions. For example, the pK_a of a carboxylic acid is normally in the range of 4−5, but when the acid functionality is presented on a monolayer, the pK_a increases with the degree of ionization and is approximately two units greater.[23] This increase is due to the electrostatic repulsion experienced by proximal carboxylate groups and is a consequence of confinement of the groups along the two-dimensional interface. In another example, we showed that the Diels−Alder reaction of cyclopentadiene with a benzoquinone group tethered to a monolayer follows different kinetic profiles when the functional group surrounding the quinone groups is varied.[19] The reaction follows well-behaved second-order kinetics when hydroxyl groups surround the dienophile but a more complex pathway consistent with initial partitioning of the diene at the interface when methyl groups surround the quinone. We also demonstrated that the steric accessibility of the reactant affects the reaction rate. For the same Diels−Alder reaction, when the immobilized quinone was presented on the monolayer by way of a short tether, the rate constant was substantially lower than when it was presented on a longer tether.[20]

It is still difficult, however, to perform mechanistic studies of organic reactions at the solid−liquid interface. One reason is that it is difficult to quantitatively measure the density of product and therefore the kinetics of interfacial reactions. For example, the most sensitive methods, based on X-ray photoelectron spectroscopy,[24] secondary ion mass spectrometry,[25] and scanning tunneling microscope,[26] are slow and not always suited to the analysis of the reaction products that are structurally similar to the reactant. More accessible methods, including ellipsometry,[27] atomic force microscopy,[28] and grazing angle IR,[29] are less quantitative and again applicable to only a fraction of reactions. Moreover, verifying the structures of reaction products remains a challenging task for

interfacial reactions. In both these respects, our development of the SAMDI mass spectrometry method is significant for studies of interfacial reactions.[22,30,31] SAMDI uses a laser to desorb the alkanethiolates from the monolayer and time-of-flight to determine their masses (or those of the corresponding disulfides). Therefore, any reaction that changes the mass of a substituent at the end of the alkanethiolate chain will lead to a product that is observed in the SAMDI spectrum. Much work has shown this method to be quantitative in analyzing monolayers[32−34] and able to be implemented in a high throughput format,[35−37] allowing tens of thousands of reactions to be analyzed in a day. In the present work, we use SAMDI to characterize the nucleophilic displacement of alkyl iodides by N-methylpyrrolidine and to obtain rate constants for the reaction in the presence of halide salts (Figure 1). This work shows a striking dependence of the reaction rate on salt concentration that has no analogue in the corresponding solution-phase reaction.
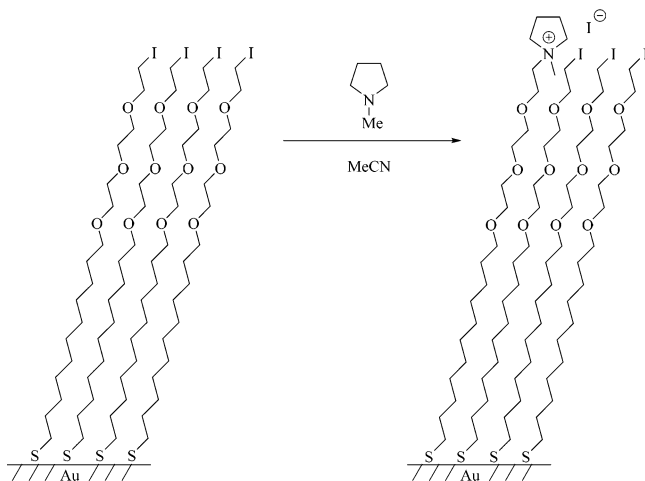

Figure 1. Reaction of an iodo-terminated self-assembled monolayer with N-methylpyrrolidine giving the corresponding N-alkyl-N-methyl-pyrrolidinium product.

■ EXPERIMENTAL SECTION

Materials and Methods. All chemicals were obtained from Sigma-Aldrich and used without further purification unless otherwise indicated. Acetonitrile (HPLC grade) was obtained from VWR International. Tetrabutylammonium chloride was obtained from TCI America. NMR spectra were acquired on a 400 MHz Agilent DD MR-400 instrument.

Synthesis of Iodide-Terminated Disulfide 3. The synthesis was performed as reported previously.[38,39] Ethylene glycol-terminated disulfide **1** was prepared as reported.[40] A mortar was charged with dry K_2CO_3 (0.2 g), disulfide **1** (40 mg), and TsCl (0.2 mmol), which was grinded vigorously for 5 min. The reaction progress was monitored by matrix-assisted laser desorption ionization (MALDI). After the completion of tosylation, remaining tosyl chloride was removed by addition of powdered KOH (2 mmol), and the product was vigorously grinded. The product was dissolved in dichloromethane (10 mL); the solution was filtered, and solvent was evaporated in vacuo. Column chromatography over silica gel (hexane/ethyl acetate = 20/1) provided the tosylate disulfide **2**. Yield 66%. Mass (MALDI): calculated for $C_{48}H_{82}O_{12}S_4$ (M + K), 1017.5; found, 1018.0.

A solution of tosylate disulfide **2** (38.4 mg) and NaI (150 mg) was refluxed in butanone (1 mL) in the dark for 10 h. The solution was filtered, and the solvent was removed in vacuo. The residue was dissolved in hexane and washed with dilute $Na_2S_2O_5$ (3×) and water

(1×) and dried over Na_2SO_4, and the solvent was evaporated. Yield: 94% of a yellow liquid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.76 (t, J = 6.9 Hz, 4H), 3.69−3.63 (m, 12H), 3.62−3.55 (m, 4H), 3.45 (t, J = 6.8 Hz, 4H), 3.26 (t, J = 6.9 Hz, 4H), 2.73−2.63 (t, J = 7.4 Hz, 4H), 1.72−1.62 (m, 4H), 1.61−1.55 (m, 4H), 1.35−1.23 (m, 28H). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 71.98, 71.53, 70.71, 70.59, 70.23, 70.05, 39.17, 29.62, 29.55, 29.51, 29.47, 29.46, 29.21, 29.20, 28.51, 26.07, 2.87. Mass (MALDI): calculated for $C_{34}H_{68}I_2O_6S_2$ (M + Na), 913.2; found, 913.7.

Preparation of Monolayer Substrates. Gold-coated coverslips (5 nm Ti, 30 nm Au) were immersed in an ethanolic solution containing 0.2 mM symmetric iodide disulfide **3** for 72 h at 4 °C. After immobilization, the glass slides were removed from solution, rinsed with water and ethanol, and then dried with a stream of nitrogen gas.

Determination of Interfacial Rate Constants. Monolayer-coated slides were cut into pieces sized approximately 1 cm^2 and placed in solutions containing a series of concentrations of N-methylpyrrolidine and salt for varying times; then the reaction was quenched by pure acetonitrile, and the slides were rinsed with acetonitrile, water, and ethanol and dried with a stream of nitrogen gas.

Mass Spectrometry. Monolayers were treated with matrix (2,4,6-trihydroxyacetophenone, 10 mg/mL in acetone), dried, and analyzed by SAMDI-MS. Mass analysis was performed using a 4800 MALDI-TOF/TOF instrument (Applied Biosystems, Framingham, MA). A 355 nm Nd:YAG laser was used as a desorption/ionization source, and all spectra were acquired with 20 kV accelerating voltage in positive reflector mode. The extraction delay was 450 ns; 500 laser shots were applied, and the entire surface of the gold piece was sampled.

Determination of Solution Rate Constants. A solution of N-methylpyrrolidine (0.2 M), iodobutane (0.2 M), and a specific amount of NaI (0, 0.1 M, 0.2 M, 0.4 M) in acetonitrile-d_3 (0.75 mL) was prepared and immediately analyzed by single-pulse ^{1}H NMR spectra taken at regular intervals. The kinetic data were obtained from integrated ratios of the reactant and product. Data were fit by least-squares analysis ($R^2 > 0.99$) according to eq 1. The slope gave the second-order rate constant k_2.

$$\frac{1}{[\text{Reactant}]_0 - [\text{Product}]_t} = k_2 t + C \tag{1}$$

■ RESULTS

Preparation of Monolayers. We first synthesized the iodo-terminated alkyl disulfide **3** by treating the tri(ethylene glycol)-terminated disulfide **1**[40] with tosyl chloride (TsCl) and potassium carbonate to generate the corresponding tosylate disulfide **2**, which was then converted to the desired disulfide **3** by substitution with potassium iodide in butanone (Figure 2). Monolayers were prepared by immersing gold-coated glass slides into an ethanolic solution of **3** (0.2 mM) for 72 h at 4 °C. The monolayers were characterized by SAMDI mass spectrometry, which showed two primary peaks at m/z of
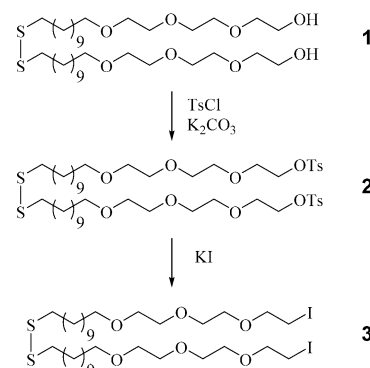

Figure 2. Synthesis of iodo-terminated alkyl disulfide.

913.3 and 929.3, corresponding to the sodium and potassium ion adducts of the iodoalkyl disulfide, respectively.

Determination of Rate Constant. We used SAMDI mass spectrometry to quantitatively follow the progression of the interfacial S_N2 reaction. In SAMDI, irradiation of the monolayer with a laser results in cleavage of the thiolate–gold bond and desorption of the alkanethiol (or the corresponding disulfide) with little fragmentation. In this way, SAMDI gives the mass of the alkanethiolates in the monolayer and can reveal changes in mass due to reactions of the terminal groups. A mass spectrum shows $M + Na^+$ and $M + K^+$ peaks for the symmetrical iodo-terminated disulfide **1** at m/z of 913.3 and 929.3, respectively (Figure 3A). Displacement of the iodide
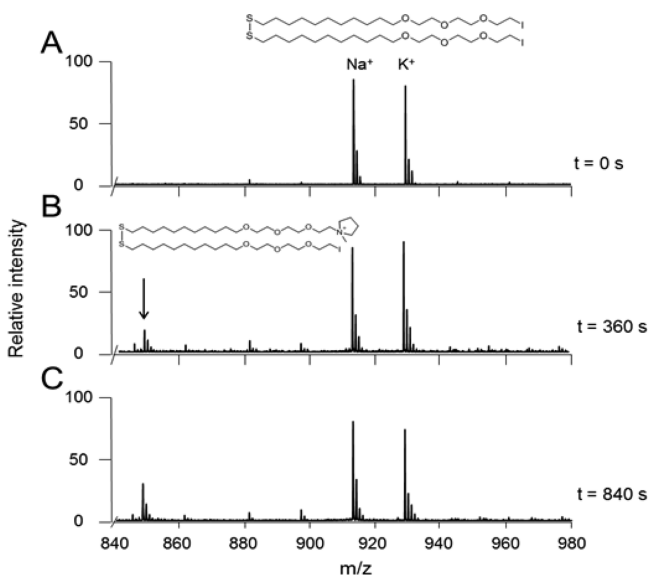

Figure 3. (A) SAMDI mass spectrum of the monolayer terminated in the iodide group. (B) A mass spectrum after 6 min of reaction with *N*-methylpyrrolidine shows a peak of $m/z = 848.0$, corresponding to the pyrrolidinium product. (C) This peak increases after 14 min of reaction.

by *N*-methylpyrrolidine reduces the mass of the alkanethiolate by 42 Da (Figure 3B). To obtain kinetic data, we cut the monolayers into chips approximately 1 cm^2 in size and placed them into solutions of the *N*-methylpyrrolidine in acetonitrile at room temperature for times ranging from 0 to 24 min and with concentrations of the nucleophile ranging from 0.5 to 5 mM. We then analyzed each monolayer by SAMDI and determined the extent of reaction using the relative peak intensity of product and substrate. The yield was determined from the ratio $I_P/(I_P + I_S)$, where I_P is the intensity of the product peak at time t, I_S the intensity of the substrate peak at time t, and t the reaction time.

Figure 4A shows a representative plot of the reaction yield, $I_P/(I_P + I_S)$, as a function of time. Because these experiments were carried out under pseudo-first-order conditions—the amount of pyrrolidine is in large excess over that of the immobilized alkyl iodide—the pseudo-first-order rate constant k' was determined by fitting the data to eq 2. We then repeated the experiment with a series of concentrations of *N*-methylpyrrolidine. A plot of the pseudo-first-order rate constants versus the concentration of the *N*-methylpyrrolidine was linear, and the best-fit slope of these data provided the second-order rate constant, 0.196 M^{-1}·s^{-1}, for the reaction.
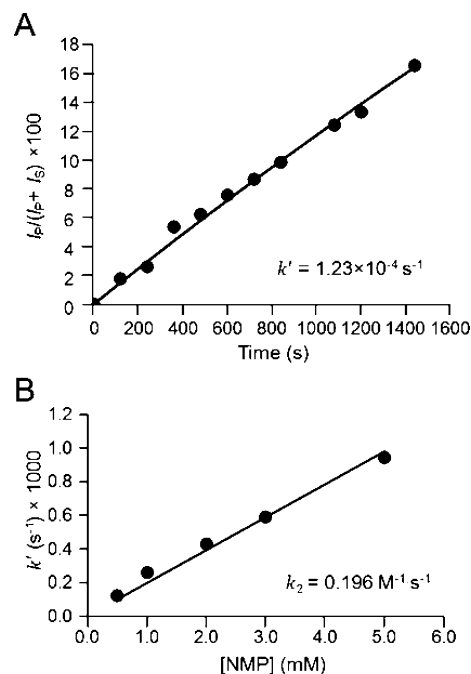

Figure 4. (A) Determination of pseudo-first-order rate constants by plotting the conversion versus time. The conversion was calculated by dividing the intensity of peaks for the product (I_P) by the sum of the intensities of the substrate (I_S) and the product. The data were fit to an exponential to give a pseudo-first-order rate constant (k') for the reaction. (B) The pseudo-first-order rate constants were plotted versus the concentration of *N*-methylpyrrolidine. The slope of the plot gives the second-order rate constant for the reaction (k_2).

$$\frac{I_P}{I_P + I_S} = 1 - e^{-k't} \tag{2}$$

Dependence of Surface Kinetics on the Concentration of Sodium Iodide. We repeated the experiment and analysis described above for reactions that included sodium iodide, at six concentrations ranging from 0.025 to 1.0 mM. The sodium iodide was predissolved in the *N*-methylpyrrolidine solution in acetonitrile before the monolayer substrates were placed in the solutions. We found that the rate constant decreased in the presence of the salt, even for concentrations as low as 25 μM. The degree of rate deceleration was greater as the concentration of sodium iodide was increased and reached a limiting value at approximately 1.0 mM (Figure 5A). To determine whether this salt effect on the substitution reaction is unique to the interfacial reaction, or whether it also operates in the corresponding solution-phase reaction, we examined the reaction of 1-iodobutane with *N*-methylpyrrolidine in acetonitrile. We used NMR to determine the extent of reaction and to measure rate constants for reactions performed in the presence of four concentrations of sodium iodide. These experiments show that iodide has a negligible effect on the homogeneous reaction (Figure 5B). Remarkably, these experiments also show that the rate constants for the homogeneous reaction are approximately 2 orders of magnitude lower than that for the interfacial reaction.

Dependence of Surface Kinetics on the Concentration of Tetrabutylammonium Halides. We next examined whether this salt effect on the interfacial reaction is observed with the other halide salts. Because sodium bromide and sodium chloride are insoluble in acetonitrile, we repeated the
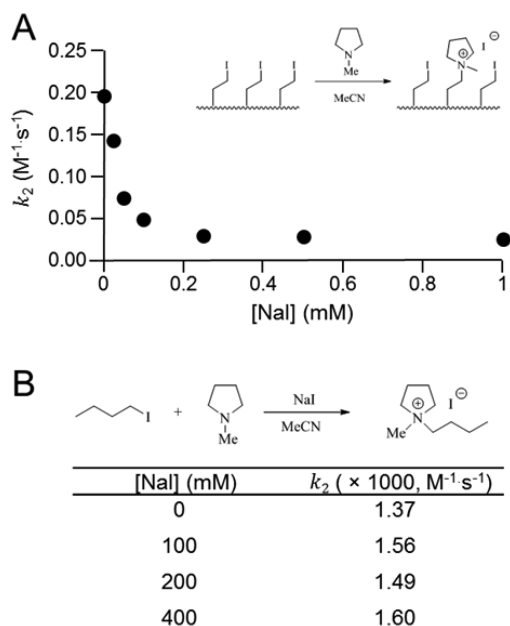
Figure 5. (A) Dependence of the second-order rate constant for the reaction of the iodo-terminated monolayer and *N*-methylpyrrolidine on the concentration of sodium iodide present in the reaction solution. (B) Rate constants were determined for the corresponding solution-phase reaction of iodo-butane with *N*-methylpyrrolidine in the presence of sodium iodide at four concentrations.

[NaI] (mM)	k_2 (× 1000, M^{-1}·s^{-1})
0	1.37
100	1.56
200	1.49
400	1.60

Figure 6. Rate constants for the interfacial reaction of the *N*-methylpyrrolidine with the iodo-terminated monolayer determined in the presence of TBAI (top, inset shows a magnified view), TBABr (middle), and TBACl (bottom).

determination of rate constants using tetrabutylammonium halides (TBAX). We again found that the reactions were well-behaved in the presence of each of the three salts, with pseudo-first-order rate constants that were fit well by the exponential function and with a linear relationship between these pseudo-first-order rate constants and the concentration of salt. However, the rate deceleration was greatest with the iodide salt, followed by the bromide and then the chloride salt. At the highest concentrations of each of the three halides, the rate decreased by a similar amount—approximately 7-fold. However, this decrease was observed at 1 mM for the TBAI salt but at 100 mM for TBABr and 1000 mM for TBACl. The dependence of the rate constant on the concentration of each salt is shown in Figure 6.

■ DISCUSSION

This work provides a well-characterized example of the extent to which an interfacial organic reaction can differ from its corresponding solution-phase analogue. The nucleophilic displacement of a primary alkyl iodide by a tertiary amine is a well-characterized and understood reaction. Yet, we find that it proceeds with a larger rate constant at the interface as compared to the homogeneous format. More striking is that the rate of the interfacial reaction decreases significantly with the addition of halide salts, with the rate being most sensitive to the addition of iodide, then bromide, and least sensitive to the addition of chloride salts. The addition of iodide leads to a 7-fold decrease in the second-order rate constant over a change in concentration of sodium iodide from 0 to 0.25 mM. The other halides must be present at higher concentrations to observe a decrease in rate constant, and those decreases are more gradual with respect to the concentration of the salt.

We do not understand the mechanistic basis by which the presence of halides reduces the rate constant of the interfacial
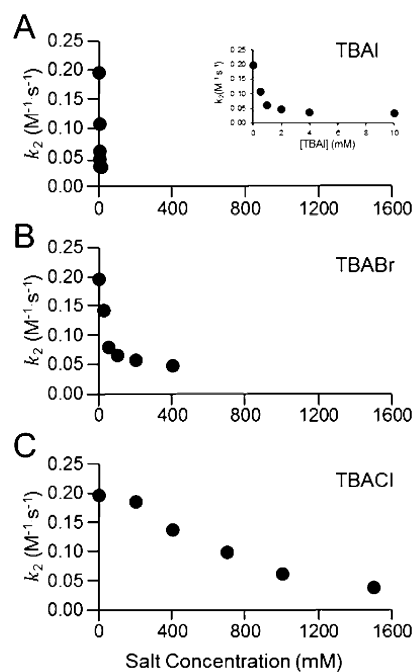
nucleophilic displacement, though we note several trends that inform the mechanistic possibilities. First, the reduction in rate observed in the presence of all three salts—iodide, bromide, and chloride—approaches a common final rate, even though the halide concentrations required to reach this limiting rate vary by a thousand-fold. This observation is consistent with partitioning of the halides to the interface, and once saturated, giving a similar effect on rate. Because the iodide salts exhibit significant impact on the reaction rate at lower concentrations than do the bromide and chloride salts, we suggest that the free energy change in transferring a halide from the bulk to the interface is most favorable for the iodide and least for the chloride. We find that this trend is consistent with the solubilities of the tetrabutylammonium halides: TBAI, for example, is the least soluble among the three salts and reduces the rate of the interfacial reaction at lower concentrations than the other salts. However, this explanation is not consistent with the effect of the sodium halide salts, where NaI reduces the reaction rate to a greater extent than does NaBr but is more soluble than the latter. It then becomes apparent that both iodide salts (TBAI and NaI) have more significant rate reduction effect than corresponding bromide and chloride salts. This difference indicates that the iodide may have a stronger affinity for the interfacial region and that this thermodynamic driving force is a more relevant measure than is the solubility of the salts. Indeed, several studies of the enrichment of halides at the air−water interface reveal that the larger halides can localize to the liquid−gas interface to a greater extent than smaller halides.[41] This trend is likely due to the greater polarizability of the larger anions and is related to the Hofmeister series, which shows that the larger halides are more effective at interaction with and denaturing proteins.[42] Hornik and Netz have performed molecular dynamics simulations to demonstrate that the halides also localize at the solid−liquid interface and that the larger, more polarizable

ions have a greater thermodynamic driving force for localization.[43]

We also considered that the size of the anions might play a critical role in the rate reduction because the interfacial reaction produces a positively charged immobilized pyrrolidinium salt that would attract counter-anions to the interface, possibly blocking nearby reaction sites. However, the kinetic data reveal that this is not the case. At the start of the reaction, when product has not yet formed, there is no charge and hence no salts at the interface, and the nature of the salt would be expected to play little role in the reaction until the accumulation of product recruits the halide counterion to the interface. However, we find that the pseudo-first-order rate constant is well-behaved, which is inconsistent with a changing rate constant as the reaction proceeds. However, when we performed the reaction in the presence of 15-crown-5, which coordinates sodium and increases the activity of the anion, we found that the reduced rate of the reaction in the presence of sodium ion is rescued and that the rate is higher than that for a reaction that does not have the crown ether in the reaction solution.

Second, we have confirmed that the addition of the bromide or chloride ion does not directly participate in the reaction by, for example, first displacing the iodide and then serving as an electrophile in the nucleophilic addition of the pyrrolidine. We know this because the SAMDI spectra during the reaction show no peaks for the accumulation of bromo- (or chloro-) substituted alkanethiols. Because the reaction is slower in the presence of these salts, we would expect that any halide-exchanged intermediates would have sufficient lifetime that they would be observed in the monolayer.

The approximately 100-fold greater rate constant for the interfacial reaction relative to its solution counterpart could have a few different origins. First, the structure of the solvent near the surface is certainly different than that in the bulk solution, because solvent molecules are not isotropically oriented at the interface and further will have different densities and physical properties than does the bulk solvent.[44] The solvent structure can also depend on the presence of salts that accumulate at the interface.[45] The different solvation of the reactants and the transition state are expected to alter the transition state energy and therefore the rate constant for the reaction. An anisotropic organization of solvent, for example, would be expected to give a higher dielectric constant at the interface, and the S_N2 reaction we study would be expected to proceed with a faster rate constant in solvents that have a higher dielectric constant, because there is accumulation of partial charge in the transition state. Second, the iodoalkyl group may be preorganized—for example, through its orientation relative to the interface—for reaction and therefore give a reaction that proceeds with a less negative entropy of activation. Quantum chemical calculations could reveal the likely basis for the observed rate constants, but these calculations still require substantial computational resources and are generally not feasible. In any event, the reaction we study here urges caution in assuming that trends obtained from homogeneous phase reactions can be applied to the corresponding interfacial reaction.

Finally, we note that the combination of monolayers and SAMDI mass spectrometry was essential to the studies described here. The monolayers provide a structurally well-defined and stable surface that offers control over the densities and environments of reactants. SAMDI provides a label-free method for observing reaction intermediates and products, quantitating the densities of these species and enabling kinetic studies of interfacial reactions. It would have been difficult to perform the studies described here using other analytical methods, either because they are not sensitive to modest changes in surface structure that accompany the reaction or because they have a throughput that would make it difficult to perform the thousands of reactions required when conducting this work. Indeed, we believe that the combination of techniques described here, SAMs and SAMDI, will provide an effective model system for the kinetic studies of a broad range of interfacial reactions and will be significant in elucidating additional factors that are unique to the interfacial reactions.

CONCLUSION

This paper describes a study of a salt effect in the kinetics of an interfacial S_N2 reaction and is significant in identifying a remarkable difference in kinetics relative to that for the same reaction in solution. The interfacial reaction had a 100-fold greater rate constant compared to the homogenous reaction. Also surprising, the rate of the interfacial reaction, but not the homogeneous reaction, decreased with the addition of halide salts, and this deceleration was dependent on the concentration and specific salt. The decreasing rate of the reaction with added salt is consistent with a partitioning of salt to the interfacial region, though the structural details of this effect await computational study. We believe that the combination of SAMs and SAMDI provides a methodology that is well-suited for understanding the physical organic chemistry of interfacial reactions.

AUTHOR INFORMATION

Corresponding Author
*E-mail: milan.mrksich@northwestern.edu.
ORCID
Milan Mrksich: 0000-0002-4964-796X
Notes
The authors declare no competing financial interest.

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ABBREVIATIONS

SAM, self-assembled monolayer; SAMDI, self-assembled monolayers for matrix-assisted laser desorption/ionization mass spectrometry

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