

The Role of the Interface in Thin Film and Droplet Accelerated Reactions Studied by Competitive Substituent Effects

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Abstract: Based on a study of competitive substituent effects in a Claisen–Schmidt reaction, interfacial effects have been shown to play an important role in accelerated reactions that occur in thin films and droplets. A role for the interface in an accelerated C–C bond-formation reaction between 6-hydroxy-1-indanone and aromatic aldehydes is indicated by cooperative interactions between *p*-methylbenzaldehyde and *p*-nitrobenzaldehyde. Additional acceleration over that occurring in bulk reactions is seen for *p*-methylbenzaldehyde, but only in the presence of *p*-nitrobenzaldehyde. A decrease in the degree of acceleration is detected when the reaction is forced electrostatically to occur inside the thin film, and the interface is shown to participate in the accelerated reactions. This experimental evidence for interfacial thin film and droplet acceleration supports a recent model and builds on earlier work which locates molecules within evaporating droplets in electro-

Reactions occurring in small-volume “reactors”, such as microcompartments in microfluidic systems,^[1] droplet suspensions in water,^[2] droplets produced by many kinds of spray methods,^[3] and thin films on surfaces,^[4] are interesting as they are much faster than the corresponding bulk-phase reactions. For example, the aza-Michael addition in thin films without catalyst shows a rate enhancement over conventional bulk solution-phase reactions.^[4a] An accelerated Hantzsch synthesis is detected by on-line mass spectrometry (MS) in charged droplets generated by electrospray.^[5] The rates of some droplet reactions are reported to be 10⁶ times faster than in the bulk.^[5,6]

Many factors may contribute to reaction acceleration, including: a) solvent evaporation with associated increases in reagent concentrations and extremes of pH values as the solvent is depleted from the droplets;^[4a,b,7] b) rapid mixing of reagents within the droplets;^[1] and c) confinement of reagents in small-volume reactors,^[6,8] especially because of the fact that small-volume reactors have large surface-to-volume

ratios. Amongst these factors, reagent confinement in small-volume reactors and particularly the role of interfacial effects is of interest in this work.

The behavior of molecules at a liquid interface^[9] (a water–air interface or a water–oil interface) can be quite different from the bulk.^[10] Differences in binding energy at the interface cause molecules to be differentially absorbed with differences depending on individual molecule/surface affinities.^[11] This behavior of molecules is exhibited in the accumulation of nanoparticles at liquid interfaces to form self-assembled structures^[12] and the adhesion of proteins at liquid interfaces to form protein crystals.^[13]

Fallah-Araghi et al. describe a non-catalytic reaction/adsorption model in which the reactants adsorb at the droplet interface (with binding energies of a few times the value of kT , where k is the Boltzmann constant), react, and diffuse back into the bulk.^[14] They propose that the adsorption of molecules at interfaces in small droplets plays an important role in accelerating reactions inside droplets.^[14] The conclusion comes from calculations based on well-known thermodynamic concepts for bulk and surface molecular reactions and surface adsorption.^[15] Even though this model has the potential to be widely applicable to accelerated reactions in confined volume reactors,^[16] direct experimental evidence is lacking: it is notably difficult to study interfacial effects in small-volume reactors, given both the size and timescales involved.

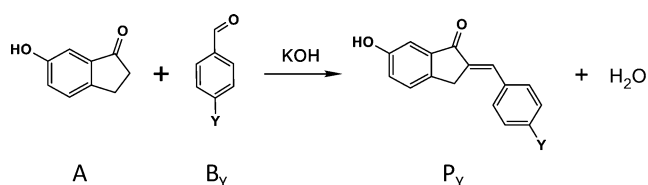
Paper spray (PS), introduced in 2010,^[17] is an ambient ionization method^[18] which has been widely used for direct MS analysis of complex mixtures.^[19] Reaction mixtures can be examined by PS-MS but it is also known that dramatically accelerated reactions can occur in thin films of reaction mixtures that are allowed to dwell on paper.^[20] Droplets generated by spray ionization methods can also be used either to analyze reaction mixtures^[21] or, for example by allowing evaporation of droplets as they move towards the MS analyzer, to cause reaction acceleration in the evaporating droplets.^[3a,b,5,6] To probe the acceleration process, PS thin films and nano electrospray ionization (nESI) droplets were used as small-volume reactors. On-line MS analysis was performed and competitive substituent effects provided access to relative reaction rates (see below). The chosen reaction was the Claisen–Schmidt base-catalyzed condensation of 6-hydroxy-1-indanone with *p*-substituted benzaldehydes (Scheme 1). This reaction is known to be accelerated in microdroplets^[3b] and on thin films.^[22] To test whether interfacial phenomena play a role in reaction acceleration in these small-volume reactors (thin film and droplets), five substituted benzaldehydes, including *p*-methylbenzaldehyde and *p*-nitrobenzaldehyde, were allowed to react simultane-

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Scheme 1. Claisen–Schmidt base-catalyzed condensation of 6-hydroxy-1-indanone with *p*-substituted benzaldehydes (Y = H, Cl, NO₂, OCH₃, CH₃).

ously with 6-hydroxy-1-indanone. This choice was made because there is a relatively strong intermolecular hydrogen bond between the methyl and nitro groups.^[23] The hypothesis is that if acceleration occurs at the interface, then the *p*-methylbenzaldehyde should get additional acceleration because more of it will be transported to the interface by its intermolecular association with *p*-nitrobenzaldehyde. This unusual effect should be reflected in the Hammett plot. (The ρ value (reaction constant) of the Hammett plot for micro-reactors should also change relative to that for the bulk reaction because of the different electronic effects in interfacial and bulk reactions.)

To measure intrinsic substituent effects, bulk-phase competitive reactions were carried out. To ensure that the ratios of product signal intensities accurately represent the corresponding reaction-rate-constant ratios (see the Supporting Information for a detailed discussion), the concentration of each substituted benzaldehyde was ten times that of 6-hydroxy-1-indanone. After 20 min of reaction, an aliquot of the reaction mixture was diluted 30 times to prevent further reaction during analysis by PS-MS (droplet or thin-film acceleration is not expected at such low concentrations of reactants and catalyst). The MS of the bulk reaction product is shown in Figure S1 in the Supporting Information. From the isolated ion currents of each product ion (Figure S2), a Hammett plot is obtained (Figure 1 a). The diluted reaction mixture was also analyzed by nESI, and the corresponding Hammett plot is shown in Figure S3. The results of analysis by PS and by nESI are identical; both give very good linearity, with ρ values of 2.17 and 2.12 (day-to-day variance ± 0.2), that agree well with each other and with a reported ρ value (2.1) for a similar bulk reaction.^[24] The similarity of the results from PS-MS and nESI-MS also suggests that no significant acceleration occurs in the detection step (if there were, the MS results of nESI and PS should be different, given differences in the two ionization methods). Thus, these data are taken to characterize the electronic effects associated with the bulk reaction.

Accelerated competitive reactions were carried out on PS thin films with proportions of reagents and base kept the same as in the bulk-phase reaction. The reagent solutions were applied on the paper triangle in front of the MS inlet and were left to dry for 1 min before the spray solvent, methanol, and voltage were applied. Significant acceleration was seen in online PS experiments (Figures S4, S5). The mass spectra of a 10 min bulk-phase competitive reaction and the corresponding 1 min PS thin-film reaction are compared in Figure S5. To explicitly answer the question of whether accel-

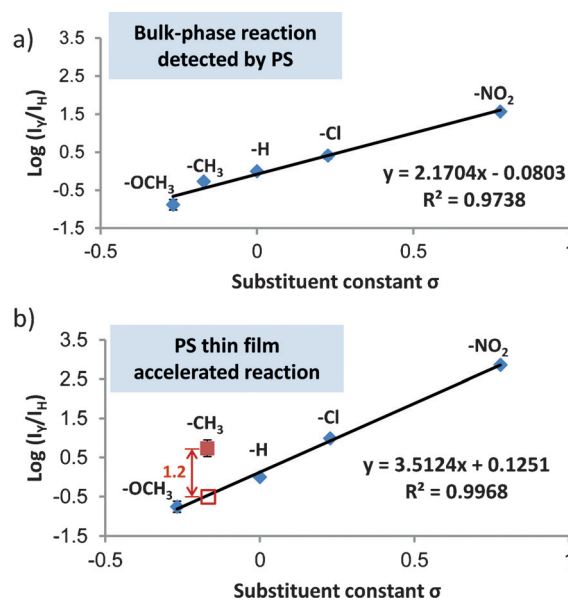


Figure 1. Hammett plots of a) bulk-phase competitive reaction detected by PSMS after 20 min reaction (mixtures were diluted 30 times before detection), and b) the PS thin film accelerated competitive reaction. In (b), the red box on the line represents the position methylbenzaldehyde should take; the bars and the number 1.2 ($\log_{10} 15$) indicate the extra acceleration. I_H is the signal intensity for the reaction product of benzaldehyde (Y = H), whereas I_Y is the signal intensity for the reaction product of substituted benzaldehyde.

eration occurs on the paper or in the evaporating droplets, an experiment was done in which offline PS and subsequent nESI analysis were performed under conditions that minimized any reaction during analysis (short droplet-transfer distances). The results of this offline experiment agree with those in Figure 1 b, which is for online PS. Data for the offline PS experiment and subsequent analysis by nESI (Figure 2) show that the accelerated PS reaction occurs on the paper rather than during droplet evaporation. The isolated ion current of each 1 min PS thin-film product ion and the corresponding Hammett plot are shown in Figure S6 and Figure 1b, respectively. Note that except for the product of *p*-methylbenzaldehyde, the other four reactions show good linearity with $\rho = 3.5$ (Figure 1b). The methylbenzaldehyde response is more than an order of magnitude higher than would be required for a linear substituent effect, expected from the operation of electronic effects alone. The extra 15-fold acceleration shows that the accelerated reactions on the thin film must be related to interfacial adsorption/reaction processes; neither evaporation of solvent nor more effective mixing can explain the anomalous methylbenzaldehyde result. There is also a large difference in ρ values between the Hammett plots for the PS thin film accelerated reaction ($\rho = 3.5$) and the bulk-phase reaction ($\rho = 2.2$). The Hammett ρ value is sensitive to reaction conditions^[25] and the difference of ρ values shows that the thin film accelerated reaction very likely occurs at the interface rather than in the bulk of the thin film, which would be expected to give a very similar ρ value to that of the bulk reaction.

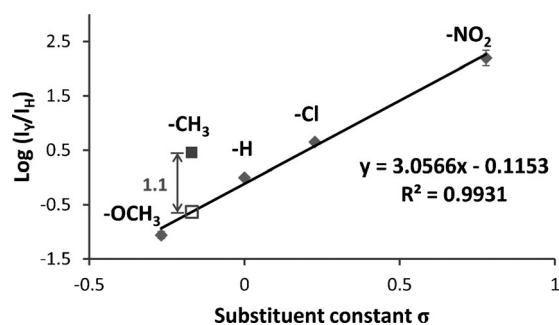


Figure 2. Hammett plot of PS thin film accelerated competitive reaction (reaction time about 1 min) with products collected off-line by washing the paper with methanol. Products were then detected by nESIMS.

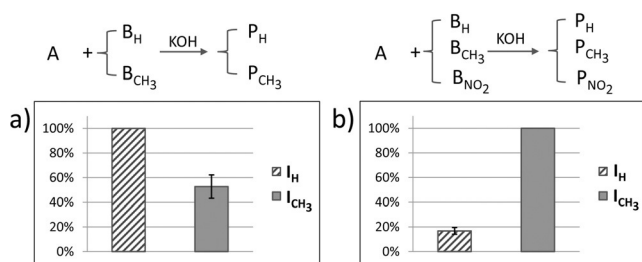


Figure 3. Relative intensities of benzaldehyde product (I_H) and p -methylbenzaldehyde product (I_{CH_3}) signals in PS thin film accelerated reactions for the a) binary competitive reaction of benzaldehyde (B_H) and p -methylbenzaldehyde (B_{CH_3}) and b) the ternary competitive reaction of benzaldehyde, p -methylbenzaldehyde, and p -nitrobenzaldehyde (B_{NO_2}) with the indanone (A).

To verify that the extra acceleration of p -methylbenzaldehyde is due to the interaction between neutral p -methylbenzaldehyde and neutral p -nitrobenzaldehyde under the conditions described above, we carried out a binary PS thin film accelerated competitive reaction of p -methylbenzaldehyde and benzaldehyde. As is shown in Figure 3a and Figure S7a, the signal intensity of the p -methyl ions is only half that of the unsubstituted case, more or less the correct ratio for a linear substituent effect. However, when p -nitrobenzaldehyde was added, the relative signal intensity of the methyl ion was about 6 times higher (Figure 3b; Figure S7b). In the bulk-phase binary and ternary competitive reactions, no such effect occurred (Figure S8). Further experimental results show that the extra acceleration of p -methylbenzaldehyde is unrelated to the presence of the other three substituted benzaldehydes (see Figure S9 and the discussion in the Supporting Information). All these results prove that the reason for the extra acceleration of p -methylbenzaldehyde is its interaction with p -nitrobenzaldehyde.

We interpret this extra acceleration as being as a result of the adsorption–reaction process: each of the reagents in the thin film undergoes its own interfacial adsorption and dissociation process. However, as the reagents are continu-

ously consumed by the reaction at the interface, more reagents arrive at the surface. As p -nitrobenzaldehyde reacts fastest (more than 100 times faster than the other benzaldehydes), more molecules of p -nitrobenzaldehyde reach the interface, some bringing p -methylbenzaldehyde with them. This increase in the transport of p -methylbenzaldehyde provides more opportunity to react and the very high reaction rate of p -nitrobenzaldehyde (circa 700 times greater than that of benzaldehyde itself), causes the extra 15-fold acceleration in the p -methylbenzaldehyde rate.

In this reaction, the rate-determining step is the reaction of the enolate negative ion with the substituted benzaldehyde (Scheme S1). To test whether application of a negative voltage during the thin film accelerated reaction would increase the rate of adsorption/reaction, we applied -2.5 kV to the paper when the reactants were applied, and after 1 min, the spray solvent, methanol, was applied and signals recorded in the negative mode. The Hammett plot (Figure S10) is similar to the PS thin film accelerated reaction without voltage, with only a slight increase for p -methylbenzaldehyde. The negative voltage fixes the enolate ions on the interface, increasing opportunities for reaction. In contrast, when forcing the enolate ions into the interior of the thin film by applying a positive voltage during the PS thin-film reaction period (1 min), both the overall degree of acceleration and the extra acceleration of p -methylbenzaldehyde is significantly affected. This is seen from off-line PS accelerated competitive reactions at -2.5 kV and $+3.5$ kV, in which products were collected on foil and detected by nESI-MS after washing and dilution in methanol. The mass spectra (Figure S11) when $+3.5$ kV is applied show less acceleration than that for the negative-voltage (-2.5 kV) PS acceleration experiment and for PS thin-film acceleration without voltage (Figure S4b). This decrease when enolate ions are forced away from the interface shows the important role that the interface plays in reaction acceleration. Figure 4a is the Hammett plot of the negatively charged off-line PS acceleration reaction. The faster reaction of the methyl reagent gives a response about an order of magnitude higher than required for the linear relationship that would be expected based on simple substituent effects. When a positive voltage was applied, p -methylbenzaldehyde only reacted twice as fast as for a linear Hammett effect (Figure 4b) and the ρ value was also much closer to the ρ value of the bulk-phase reaction, showing that a non-interfacial reaction occurs when the enolate ions are kept from the interface. Droplet accelerated competitive reactions were also examined by nESI-MS and similar results were obtained, again showing that interfacial processes are involved in reaction acceleration. Detailed results and discussion are provided in the Supporting Information.

In summary, by examining competitive substituent effects and following the interaction between p -methylbenzaldehyde and p -nitrobenzaldehyde, we show that in small thin films and droplets (in air) interfacial processes play an important role in accelerating reaction rates. This experimental evidence should help further in revealing the acceleration mechanism of small-volume reactors and thus in applying accelerated reactions more effectively and widely.

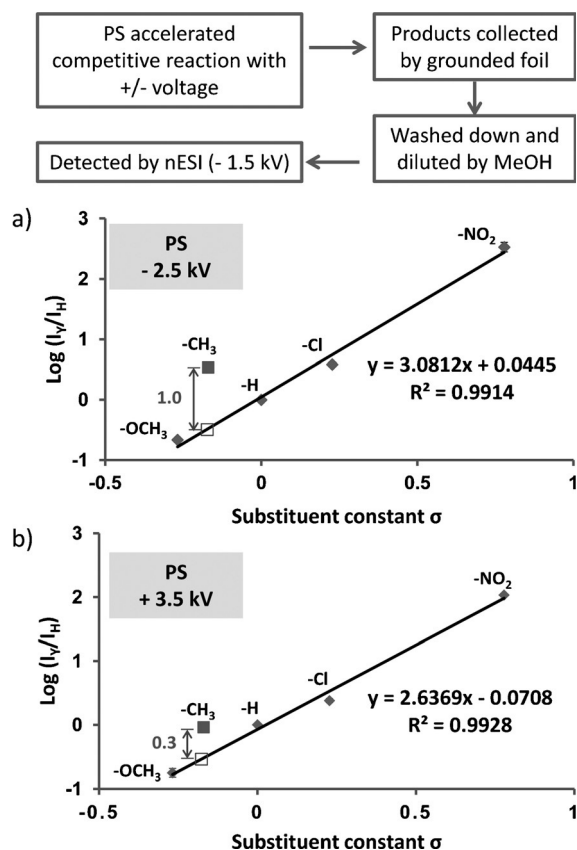


Figure 4. Hammett plot for the off-line PS accelerated competitive reaction after application of a spray voltage of a) -2.5 kV or b) $+3.5$ kV. The thin film had a dwell time of 1 min on paper to allow the reaction to occur. The analysis was carried out off-line to allow quenching of the reaction mixture before analysis.

Experimental Section

For PS thin film accelerated competitive reactions, 6-hydroxy-1-indanone ($1 \mu\text{L}$ of a 0.1M solution), KOH ($1 \mu\text{L}$ of a 1.8M methanolic solution), and a mixture containing equimolar amounts of benzaldehydes (a total $10 \mu\text{L}$ of the substituted benzaldehydes mixture, the concentration of each substituted benzaldehyde in the mixture was 0.1M) were applied onto a previously prepared paper tip and then were left to dry for about 1 min. The spray solvent (methanol) and -2.5 kV were then applied to the paper tip. For off-line negatively charged or positively charged PS thin film accelerated reactions, the voltage was applied at the same time as addition of the benzaldehyde mixture to ensure that the accelerated reactions occur under controlled voltages. A Thermo Fisher LTQ mass spectrometer (Thermo Scientific Inc., San Jose, CA) was used for these experiments. The substituent constants are obtained from Ref. [26].

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