Low-Temperature Flow NMR Investigation of the Transient Intermediate in the Nucleophilic Aromatic Substitution of 2,4,6-Trinitroanisole by *n*-Butylamine[1c]

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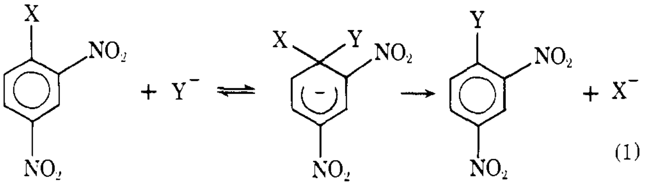
Abstract: High-resolution flow NMR has been used at low temperatures to detect and to characterize the transient intermediate δ complex on the reaction pathway in the nucleophilic aromatic substitution reaction of 2,4,6-trinitroanisole by *n*-butylamine in a solvent mixture of 50% Me_2SO-50% MeOH.

Introduction

The "two-step" mechanism for nucleophilic aromatic substitution reactions of activated aromatic compounds originally proposed by Bunnett[2] involves the formation of a cyclohexadienyl intermediate δ complex **1** (eq 1). A considerable body of kinetic evidence has been presented in favor of this general type of mechanism,[3] and indirect support comes from the many investigations of "Meisenheimer complexes",[4] species of the same general electronic structure as that of the intermediate **1**. These are usually generated by the attack of a nucleophile on an unsubstituted nitroaromatic so that the further reaction of **1** is very unfavorable (e.g., X = H in eq 1), or attack on substrates so that the leaving group is the same as the attacking group (e.g., X = Y = OCH_3 in eq 1). In both cases, the two-step eq 1 is effectively simplified to a single step. The "intermediate" may then be sufficiently stabilized to be observed spectroscopically by the use of several electron-withdrawing groups and by dipolar aprotic solvents. Different Meisenheimer complexes are found to have characteristic UV-visible absorption spectra, but NMR has been found to be the best diagnostic technique for their identification.[4] Although there are many studies of these complexes, there have been few reports of the direct observation of species of type **1** during the course of actual substitution reactions owing to their very limited lifetimes under these conditions.[5] An early report of the intermediate from the attack of azide ion on *p*-fluoronitrobenzene[6] has been shown to be erroneous.[7] A more recent report based on UV-visible spectroscopy was of the intermediate **2** formed by attack of methoxide ion on picryl chloride.[8] Crampton has shown by NMR that in fact the absorption was probably due to species **3** where the attack has occurred at the 3 position,[9] although the conditions of the two experiments were somewhat different. This illustrates the possible difficulties involved in the assignment of structures solely on the basis of UV-visible spectroscopy.



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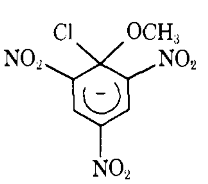

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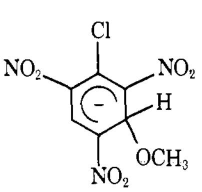

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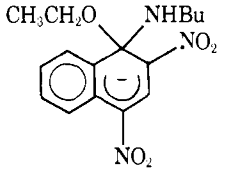
The best authenticated report of such complexes during an actual substitution reaction is the work of Bunnett and Orvik, who reported the observation of species **4** by UV-visible spectroscopy during the reaction of 1-ethoxy-2,4-dinitronaphthalene with *n*-butylamine in Me_2SO solution.[10] The final product was that of substitution of the ethoxy group by *n*-butylamine and the rate of decomposition of the intermediate was equal to the rate of appearance of product. The UV spectrum was similar to that of known Meisenheimer complexes in the dinitronaphthalene series, but on this evidence alone, it is possible that the complex formed could have been from attack at carbon 3 in the ring between the two nitro groups.



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Sekiguchi has claimed on the basis of NMR data that species of type **4** are stable at room temperature when secondary rather than primary amines are used as nucleophiles.[11]

The difficulties involved in unambiguously characterizing species of general type **1** during actual substitution reactions are their limited lifetimes and the relatively nondiagnostic character of UV-visible spectroscopy. In our laboratory we have developed the technique of flow NMR which enables high-resolution NMR spectra to be obtained from flowing chemically reacting mixtures in times as short as 50 ms after mixing.[12] It has been successfully applied to the detection and characterization of transient species in several different chemical reactions.[13] In particular, it was able to unambiguously characterize the complex observed by Bunnett and Orvik as indeed being species **4**.[14] The purpose of the present work was to use this technique in addition to more conventional ones to try to observe and to characterize species of type **1** during a nucleophilic aromatic substitution reaction where the NMR spectra of the species involved would be relatively simple.

The system chosen for study was the reaction of 2,4,6-trinitroanisole (TNA) with primary amines, as it was judged from the present literature that it was the best approximation to the general nucleophilic substitution reaction that would be amenable to this approach. The present shortest time between mixing and observation (of ~50 ms) is close to the lower limit for this type of experiment and it was felt that the next step in the development of this technique for the detection of transient

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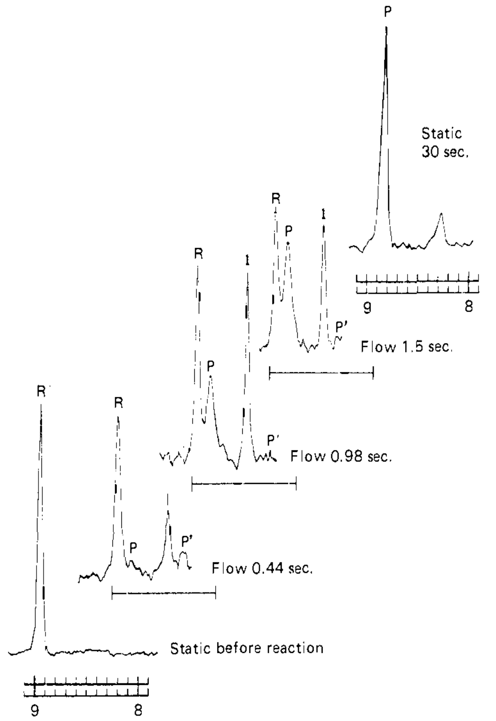


Figure 1. Flow NMR spectra recorded during the reaction of TNA (0.25 M) in 50% Me_2SO–50% MeOH with *n*-butylamine (0.5 M) at −40 °C in 50% Me_2SO–50% MeOH. The peaks assigned to reactant (R), intermediate (I), and product (P,P′) species are indicated. Bottom spectrum: static spectrum of TNA ring proton absorptions. Second spectrum: flow NMR spectrum recorded at a flow rate of 72 mL/min (0.44 s after mixing). Third spectrum: flow NMR spectrum recorded at a flow rate of 32 mL/min (0.98 s after mixing). Fourth spectrum: flow NMR spectrum recorded using a 3-cm riser and a flow rate of 32 mL/min (1.5 s after mixing). Top spectrum: static spectrum recorded 30 s after stopping the flow.

species would lie in the use of very low temperatures. To this end, a suitable binary solvent mixture was used in the investigation.

Experimental Section

All chemicals used were from commercial sources or were prepared by literature methods and had melting points in agreement with published values and NMR spectra consistent with their proposed structures.

All ^1H NMR spectra were obtained using a Varian H.A. 100 spectrometer and ^{13}C NMR spectra were obtained using a Varian CFT 20 pulse-FT spectrometer. UV-visible spectra were obtained using a Unicam SP 800 spectrophotometer. Flow NMR and UV-visible spectra were obtained using the techniques and equipment previously described.[12] Low-temperature flow NMR spectra were obtained by precooling both reactant streams in a Dewared low-temperature bath in the fringe of the magnetic field, then passing them through the field, into the high-pressure mixing chamber and through the flow NMR tube for detection. The temperature of the flow NMR tube within the probe itself was controlled by a regulated flow of cooled nitrogen gas.

Results and Discussion

The method outlined in the Experimental Section to achieve the very low temperatures used in the present study allows the reactant streams much less time to equilibrate in the magnetic field than the previous equipment used for studies above 0 °C and has the potential drawback that the relative intensities of the different signals might be unreliable if there are large differences in relaxation times for different nuclei. This may be checked experimentally by relating the intensities to that of a reference signal as a function of flow rate and also by checking for the constancy as a function of flow rate of the relative intensities of signals thought due to nuclei in the same molecule. However, in general, T_1 decreases as the temperature decreases,[15] so the nuclei need a much shorter time to equilibrate in the field. For example, the ring protons of TNA have a relaxation time of ~4 s at 30 °C in 50% Me_2SO-d_6–50% MeOH-d_4 (by volume) and this drops to ~1 s as the temperature is lowered to −40 °C (nondegassed samples). Thus lowering the temperature expedites the magnetization of the nuclei in the field. In the present work small quantities of radicals are produced, so T_1 is probably even shorter. No effects were observed that could be attributed to incomplete premagnetization of the nuclei.

The solvent system used in all of the experiments was 50% Me_2SO–50% MeOH (by volume). This mixed system was chosen as it allows measurements to be made down to −45 °C and all the species involved in the reaction are soluble in it. It was also thought to contain enough Me_2SO to stabilize any charged intermediate species formed, as the stabilities of the δ complexes in these systems are known to be very dependent on the presence of dipolar aprotic solvents. Spectra were obtained at TNA-*n*-butylamine ratios of 1:2, 1:3, and 1:4 at temperatures of −40, −30, and −20 °C.

Low-Temperature Flow NMR Measurements. A. TNA + *n*-Butylamine (1:2). Figure 1 shows the results of a typical run utilizing the flow system on the above reaction mixture. The bottom spectrum shows the single signal at δ 9.0 due to the two equivalent ring protons in TNA before reaction. Subsequent spectra are of the same spectral region, recorded on the flowing chemically reacting mixture at the flow rates and times after mixing indicated in the figure, and show, in addition to the peak for the reactant, a new peak at δ 8.5 due to an intermediate species and a peak at δ 8.8, which can be identified as the major product species by comparison with the last spectrum in the series, which is that of the static solution at equilibrium. As the flow rate is increased, that is, the time between mixing and observation reduced, there is less conversion to the intermediate species as indicated in the figure. On stopping the flow, the spectrum immediately changes to the last spectrum in the series which shows a large single absorption at δ 8.8 due to the final stable product species. The transformation to product is extremely fast and indicates that the NMR spectrum of the intermediate species could only be obtained using these techniques. By variation of the flow rate and by the introduction of "spacers", the time between mixing and observation can independently be altered[12] and the complete time evolution of the reaction mixture can be determined. The results of this at −40 °C are shown in Figure 2.

The data are complicated by the occurrence of a minor product in the reaction mixture. The concentration of this species is relatively low and is monitored from the area of a peak thought to be due to only one proton so the estimates of its concentration are relatively poor, especially in the early stages of the reaction. The nature of this product species and the time dependence of the peak at δ 8.3 ppm will be discussed in detail subsequently. The occurrence of this product in no way changes the general conclusions regarding the reaction but does limit somewhat the accuracy of the measurements of the concentrations of the three major species. As can be clearly seen from the figure, the concentration of the intermediate reaches a maximum between the disappearance of the reactant and the appearance of product, consistent with it being an intermediate on the reaction pathway between these two species. It is very short lived, even under these extreme conditions of stabilization by solvent and low temperature, reaching a maximum concentration 1 s after mixing, and thus its observation and characterization by NMR could only be made using the technique of flow NMR. Qualitatively similar results are obtained at higher temperatures, the intermediate being even shorter lived. Care must be taken in the assignment of structures to the product and intermediate species observed in the

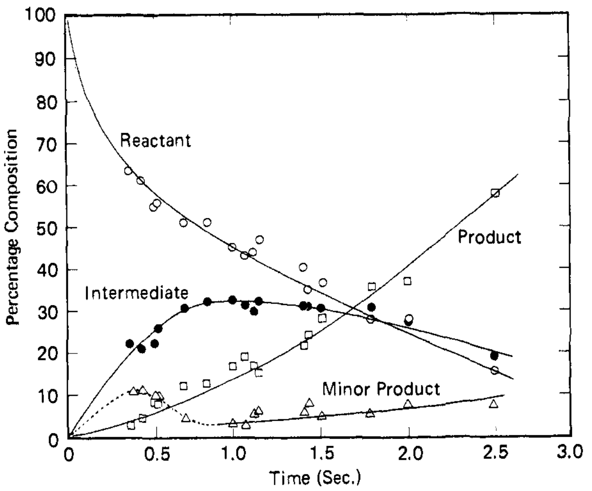


Figure 2. Percentage composition of the reaction mixture from the reaction of TNA (0.25 M) with *n*-butylamine (0.5 M) at −40 °C in 50% Me_2SO-50% MeOH as a function of time showing: ○, the disappearance of the reactant species; ●, the appearance and disappearance of the intermediate; □, the appearance of the major product species. △ indicates the approximate quantity of the minor product species.

flow NMR experiments as only single absorptions are observed for each. This indicates clearly that attack must have taken place at position 1 on the ring (i.e., at the carbon bearing the methoxy group) or (although much less likely) at C_4 or the nitro group attached to it since attack at C_3 would give rise to two sorptions of equal intensity at approximately δ 8.5 and 5.5. Attack on the ortho nitro groups would give a similar inequivalence for H_3 and H_5.

A product was isolated in quantitative yield by addition of the reaction mixture to water or dilute acid. This was identified as *N*-*n*-butylpicramide from its melting point and NMR spectrum. If the product in the reaction mixture itself were *N*-*n*-butylpicramide, it would be in the presence of 1 equiv of excess amine. It is known[15,16] for *N*-methylpicramide that methoxide ion may give proton abstraction and also nucleophilic attack at C_3 and these must be considered in the present instance. The chemical shift of the ring protons in the product (δ 8.79 ppm) is slightly different from that of *N*-*n*-butylpicramide dissolved in 50% MeOH-50% Me_2SO (δ 8.84 ppm) and it was thought that the species might be present in equilibrium with some of its conjugate base anion. This was further investigated using ^{13}C NMR. The spectrum of the product in 50% Me_2SO-50% MeOH at − 40 °C shows four absorptions in the aromatic region at δ 89.0, 94.6, 97.9, and 104.5 ppm with respect to the center of the Me_2SO-d_6 multiplet as reference. Addition of 1 equiv of amine causes no changes that could be attributed to the formation of the conjugate base, although there is the appearance of peaks which can be identified as being due to the minor product (see on). Thus, although there is presumably some conjugate base present, it must be a very small amount.

Thus it is thought that a true nucleophilic aromatic substitution reaction has taken place as indicated in eq 2 and that the intermediate observed is species **6**, the Meisenheimer complex "on the substitution pathway." The species is unfortunately too short lived to obtain ^{13}C NMR spectra, but there is indirect confirmatory evidence from such measurements in the case of attack by secondary amines, where the complexes are much longer lived (see following paper).

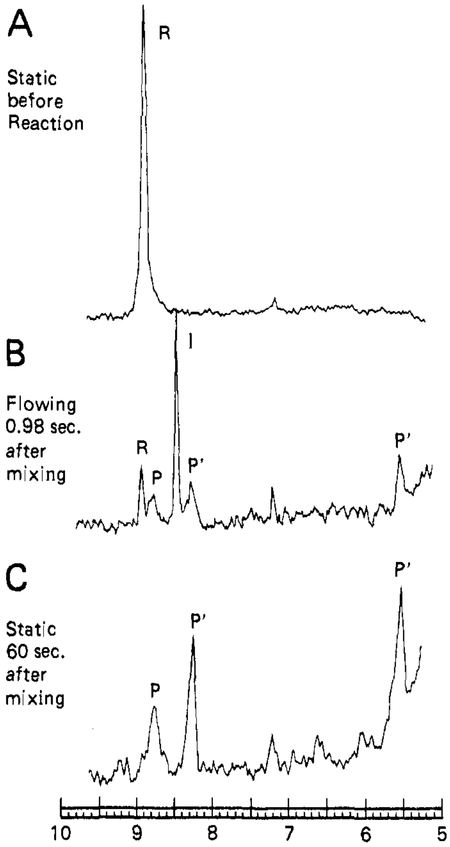
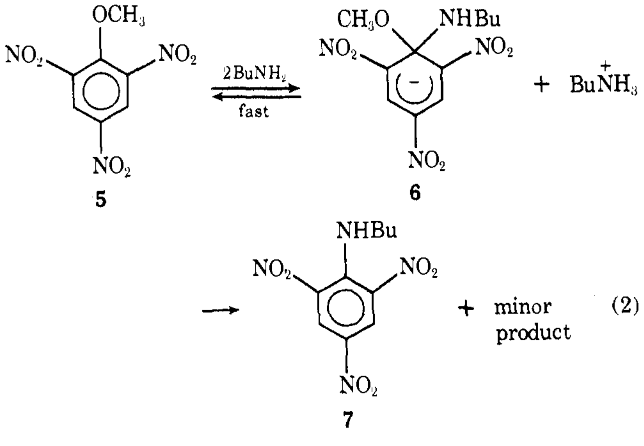


Figure 3. Flow NMR spectra recorded during the reaction of TNA (0.25 M) with *n*-butylamine (1.0 M) at −40 °C in 50% Me_2SO-50% MeOH. Top spectrum: static spectrum of TNA ring proton absorptions. Second spectrum: flow NMR spectrum recorded at a flow rate of 32 mL/min (0.98 s after mixing). Bottom spectrum: static spectrum recorded 60 s after stopping the flow.



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B. TNA + *n*-Butylamine (1:3 and 1:4). Low-temperature flow NMR measurements at −40 °C from a typical run with a TNA-amine ratio of 1:4 are shown in Figure 3. There is the immediate decrease in the intensity of the peak due to the ring protons of TNA and the appearance of new absorptions due to the intermediate and product species. The intermediate **6** may be identified as the peak at δ 8.5 as previously. On stopping the flow, there is an almost instantaneous conversion to products yielding the third spectrum in Figure 3. This spectrum is different from that obtained previously, consisting of two peaks of equal intensity at δ 8.3 and 5.55 and a third peak at δ 8.9. This latter peak is due to the neutral product and at higher amine:TNA ratios decreases relative to the other two. The latter two peaks were present in the previous spectra using a twofold excess of amine and are due to the minor product, but were much smaller in that case. The spectrum of a solution of *N*-*n*-butylpicramide in the presence of a twofold excess of amine in 50% Me_2SO-50% MeOH at the same temperature is identical with the last spectrum in Figure 4. The two peaks of equal intensity may thus be assigned to a complex resulting

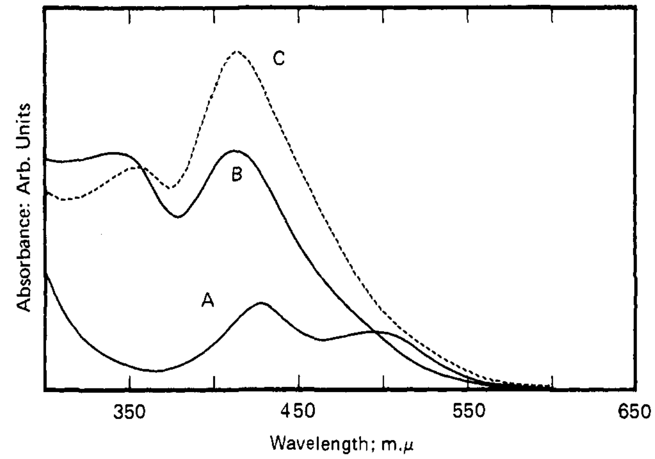
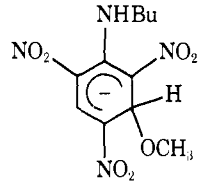


Figure 4. Flow UV-visible spectra recorded during the reaction of TNA with *n*-butylamine. Curve A: flow UV-visible spectrum recorded during reaction of TNA with 0.04 M *n*-butylamine in 50% Me_2SO-50% MeOH at −40 °C at a flow rate of 32 mL/min (~0.4 s after mixing). Curve B: UV-visible spectrum recorded on the same solution as curve A, immediately on stopping the flow. Curve C: UV-visible spectrum recorded immediately on stopping the flow with a 1:4 ratio of TNA:*n*-butylamine.

from attack on the 3 position of the substituted picramide. Whether the attack has been by the amine or methoxide (generated from the methanol solvent) is not unambiguously indicated by the spectra, although the chemical shift of the absorption at δ 5.55 assigned to the hydrogen attached to the sp^3-hybridized carbon is closer to that expected if an amino group were attached to this carbon than if an alkoxy group were attached. That the attached group is amino is confirmed by taking *N*-*n*-butylpicramide in 50% Me_2SO-50% MeOH and adding excess methoxide ion in 50% Me_2SO-50% MeOH. A single signal at δ 9.0 due to the substrate is seen with a multiplet centered at δ 8.25 due to the conjugate base, together with two absorptions of equal intensity at δ 8.47 and 5.88 due to the ring protons of the δ complex **8** by attack of methoxide ion on C_3. These shifts are similar to those previously observed for the C_3 adduct of methoxide ion with *N*,*N*-dimethylpicramide.[4] Further, if *n*-butylamine is now added to the solution, these two singlets are gradually replaced by two new singlets of equal intensity at δ 8.30 and 5.55 identical with those of the final reaction mixture shown in Figure 3. Thus the second product species is thought to be the δ complex **9** from attack of *n*-butylamine on C_3 of the neutral product. ^{13}C NMR measurements confirm that attack has taken place at C_3. Thus the ^{13}C spectrum at −40 °C in 50% Me_2SO-50% MeOH shows five ring carbon absorptions at 71.5, 77.0, 89.0, 96.0, and 113.8 ppm relative to the center of the multiplet from Me_2SO-d_6 and an additional signal at δ −14 assignable to the sp^3 hybrid carbon in **9**. Since 2 mol of amine is required to form **9** from the initial product of the reaction, **7**, it is reasonable that **9** should be favored only at higher relative amine concentrations.



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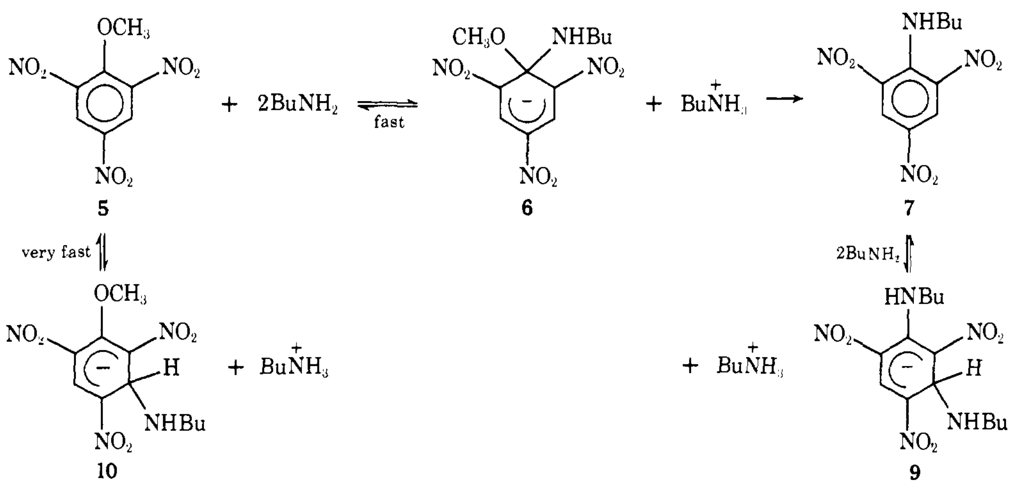
As in the previous case (2:1 ratio of amine:TNA) the time dependences of the concentrations of the various species in the reaction can be determined, although the profiles are not as well characterized at short reaction times. The curve due to the intermediate again rises to a maximum between the disappearance of the reactant and the appearance of the product species, again indicating that it is indeed the complex on the reaction pathway. The curve for the appearance of the two absorptions at δ 8.3 and 5.5 (which in the final reaction mixture are assigned to **9**) rises to an anomalously high value in the early stages in the reaction when the intensity of the low-field absorption is taken, simultaneous with the fast disappearance of the reactant, and then drops off before rising gradually to its eventual equilibrium value. Such a situation can also be seen at early reaction times in Figure 2 (open triangles, dotted portion of curve), although it is much less pronounced. It is thought that the TNA is in equilibrium through a fast reaction with the adduct from amine attack at C_3 and that this species **10**, since it would have a very similiar ^1H NMR spectrum to that of **9**, would be indistinguishable from **9** within the reduced resolution of the flow NMR experiment. Thus, in the early stages of the reaction, this peak monitors mainly the concentration of **10** and at longer times mainly that of **9**. This effect will become more pronounced at higher amine:TNA ratios.

Implicit in the assignment of eq 3 to the reaction mechanism at higher amine concentrations is that quenching the final reaction mixture with aqueous acid should again yield only *N*-*n*-butylpicramide as product since the additional product **9** should also yield this species. This has been confirmed, and the product characterized by its melting point and NMR spectrum.

The complete reaction is thus thought to be that represented by reaction 3.

Low-Temperature Flow UV-Visible Spectroscopic Measurements. Low-temperature flow UV experiments were performed on this system firstly to check the general conclusions of the flow NMR experiments regarding the reaction scheme



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and secondly to attempt to assign the UV-visible spectra of the species identified by the NMR experiments to facilitate further, more detailed study of the system in dilute solution by UV-visible spectroscopy.

Because of the extremely large extinction coefficients in these systems, it was not possible to exactly duplicate the concentrations used in the NMR experiments. It was possible to obtain spectra using the short path length flow UV-visible cell previously described[13b] using a maximum TNA concentration of 0.025 M with 0.05 M *n*-butylamine. The results of these flow UV-visible measurements are shown in Figure 4. Under flowing conditions at low temperatures with an amine:TNA ratio of 2:1, a spectrum is observed with $\lambda_{1\text{max}}$ 430, $\lambda_{2\text{max}}$ 500 nm, characteristic of a 1,1-disubstituted Meisenheimer complex.[4] Immediately on stopping the flow, this spectrum disappears and is replaced by a single absorption at 418 nm. The intermediate species observed is thus thought to be the Meisenheimer complex **6** where attack has taken place at C_1. When higher ratios of amine:TNA are used (e.g., 4:1) the absorption (λ_{max} 418 nm) thought due to the complex **9** is larger when the flow is stopped (Figure 4), consistent with the results of the NMR studies.

Conclusions

It is thought that the use of flow NMR techniques has unambiguously identified the reaction intermediate in this nucleophilic aromatic substitution and has made possible the assignment of the UV-visible spectra of all the species in the reaction, and is strong evidence in favor of the "two-step" mechanism proposed by Bunnett. In this case, the decomposition of the intermediate is clearly the "rate-determining step" in the reaction. The overall reaction is quite different from that where secondary amines are used under the same conditions (see following paper), although in the latter case it is thought that complexes analogous to **6** are initially formed. It appears that steric interactions in the transition state of the second step of the reaction may be the difference between the two systems.

It would be useful to examine the effect of leaving groups and added conjugate acid on the stability of the intermediate **6** in order to further investigate this reaction. These measurements would be best made by UV-visible spectroscopy in dilute, more ideal solutions using the spectral assignments presented in this paper. It would also be advantageous if techniques could be developed to obtain ^{13}C spectra in flowing systems with adequate efficiency and these used to check the conclusions from the ^1H flow data presented here.

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