Low Temperature Flow Nuclear Magnetic Resonance Detection of Transient Intermediates on the Actual Reaction Pathway in Nucleophilic Aromatic Substitution

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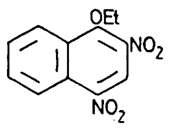
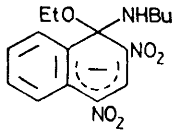
Summary The intermediate σ-complexes on the reaction pathway in the nucleophilic aromatic substitution reactions of 1-ethoxy-2,4-dinitronaphthalene (**1**) and 2,4,6-trinitroanisole (**5**) with n-butylamine have been observed and characterized by high-resolution flow n.m.r. spectroscopy at low temperatures, and their u.v.–visible spectra assigned.

There has been considerable interest in the mechanism of nucleophilic aromatic substitution reactions,[1] particularly in the applicability of the two-step mechanism proposed by Bunnett[2] in which an intermediate σ-complex is postulated. Much work has been done in recent years on the structures and properties of Meisenheimer complexes[3] which are formally analogous to these intermediate species, but there have been few reports of the detection of the intermediates themselves during substitution reactions.



(1)



(2)

Bunnett and Orvik[4] have clearly detected by u.v.–visible spectroscopy an intermediate species in the reaction of 1-ethoxy-2,4-dinitronaphthalene (**1**) with n-butylamine to which they assigned structure (**2**). The reaction of (**1**) with secondary amines was subsequently investigated by Sekigushi and his co-workers[5] who claimed on the basis of n.m.r. evidence that the species analogous to (**2**) are quite stable at ambient temperatures when secondary rather than primary amines are used.

We have developed the technique of flow n.m.r. spectroscopy[6] which enables high-resolution n.m.r. spectra to be obtained in flowing, chemically reacting systems and have found it useful in the detection and characterization of a wide variety of transient species.[7] In the present work we have applied this technique to try to characterize (**2**) and analogues species formed 'on the reaction pathway' in nucleophilic aromatic substitution reactions. In addition, we have used mixed solvent systems to attain low temperatures for these measurements in an attempt to increase the life-times of such species.

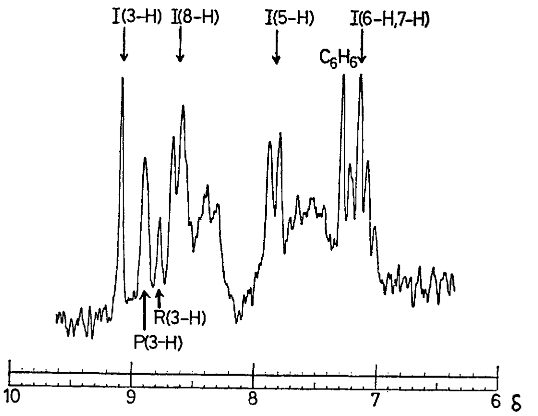
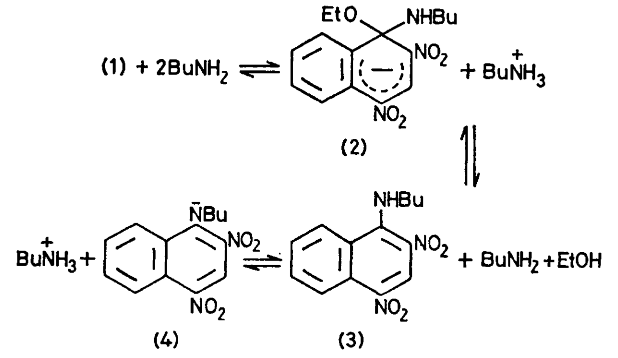


FIGURE 1. 100 MHz flow n.m.r. spectrum recorded during reaction of 1-ethoxy-2,4-dinitronaphthalene (**1**) (0·2M in 75% Me$_2$SO–25% MeOH) with n-butylamine (0·8M in 75% Me$_2$SO–25% MeOH) at 0 °C recorded at a flow rate of 32 ml min^{-1} (0·98 s after mixing). The resonances assigned to the intermediate (I) species (**2**) are indicated as are the signals due to 3-H in the reactant (R), (**1**) and product (P) (**3**) in equilibrium with (**4**). The small single peak in the spectrum at δ 7·3 is due to benzene present in the Me$_2$SO and was used as an additional marker to calibrate the spectrum.

Figure 1 shows the n.m.r. spectrum of the flowing, chemically reacting system of (**1**) (0·2M) in 75% Me$_2$SO–25% MeOH plus n-butylamine (0·8M) in 75% MeSO–25% MeOH at 0 °C recorded at a flow rate of 32 ml min^{-1} (0·98 s after mixing). The temperature and solvent composition used was a compromise determined by the limited solubility of (**1**). From a knowledge of the spectra of the reactant and product species, the spectrum of the intermediate may be identified as indicated in Figure 1 : δ 9·09 (s, 3-H), 8·62 (d, *J ca.* 8 Hz, 8-H), 7·83 (d, *J ca.* 8 Hz, 5-H), and 7·14 (m, 6- and 7-H). The proportions of the reactant, intermediate, and product species may be varied by variation of the flow rate, confirming this assignment. The absorptions due to 3-H in the reactant and product species are also indicated in Figure 1. On stopping the flow, the spectrum immediately changes to that of the final product mixture. The concentration of the intermediate species reaches a maximum after 1 s and it has a lifetime of only a few seconds under these conditions and thus its spectrum could not be measured using conventional techniques. The spectrum of the intermediate species is in general agreement with that expected for a σ-complex from a 2,4-dinitronaphthalene derivative[3d,e] showing high-field shifts due to the presence of the negative charge. Of particular interest in the assignment of structure to the complex is the appearance of the resonance due to 3-H at low field, indicating that the attack of the amine must have been at C-1 and not C-3 and the intermediate is thus unambiguously identified as (**2**) as proposed by Bunnett and Orvik.[4] The final product mixture is identified as an equilibrium mixture of (**3**) and (**4**) and the spectral changes are in complete agreement with the reactions in Scheme 1, as previously proposed, clearly indicating the applicability of the two-step mechanism in this case.†



SCHEME 1

A similar situation exists in the reaction of 2,4,6-trinitroanisole (TNA) (**5**) with n-butylamine. Figure 2 shows the

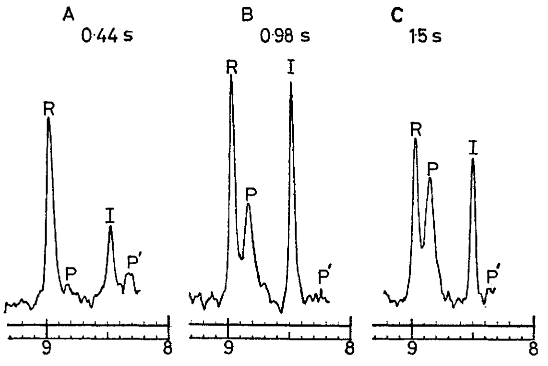


FIGURE 2. 100 MHz flow n.m.r. spectra recorded during the reaction of 2,4,6-trinitroanisole (0·25M in 50% Me$_2$SO–50% MeOH) with n-butylamine (0·5M in 50% Me$_2$SO–50% MeOH) at −40 °C showing the signals due to the aromatic protons in the reactant (R) (**5**), intermediate (I) (**6**), and product (P) [mainly (**7**)] species at various times after mixing. A: 72 ml min^{-1} (0·44 s after mixing) B: 32 ml min^{-1} (0·98 s after mixing) C: 32 ml min^{-1} using a 3 cm riser (1·5 s after mixing). The very small peak marked (P′) is due to (**9**) and increases in intensity when higher amine–trinitroanisole ratios are used.

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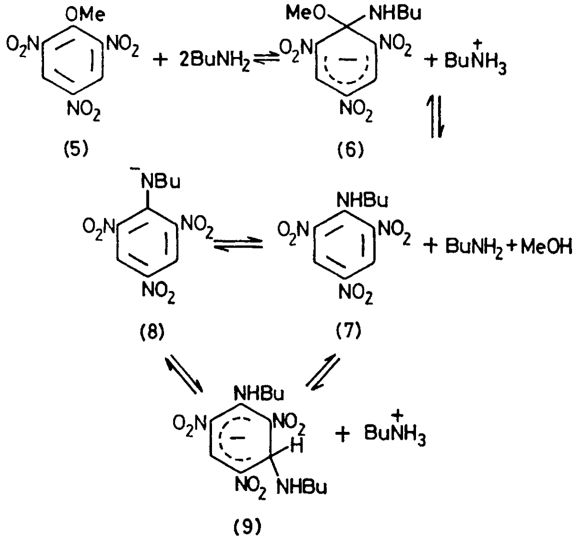
† It must be emphasized that the detection and identification of any species in a reaction mixture does not 'prove' that it is involved in the reaction pathway to yield the final product as it could exist in a side equilibrium.

low-field resonances observed for the fast-flowing, chemically reacting mixture of (**5**) (0·2 M) in 50% Me_2SO–50% MeOH with n-butylamine (0·4 M) in 50% Me_2SO–50% MeOH at −40 °C at various times after mixing. The signals due to the reactant (R) and product (P) species occur at δ 8·98 and 8·85, respectively and can be identified in the mixture as indicated in Figure 2. The additional signal at δ 8·49 is assigned to the ring protons of the intermediate σ-complex (**6**). There are no peaks in the region of δ 6 eliminating the possibility of attack at C-3. The u.v.–visible spectrum recorded under these conditions is also characteristic of a Meisenheimer complex. The proportions of all three species depend markedly on the flow rate, the intermediate reaching a maximum concentration 1 s after mixing. Again, the spectrum of the product mixture only is observed immediately on stopping the flow, indicating that the spectra could only be obtained using these techniques. The product mixture for a 2:1 amine:TNA ratio consists of *N*-(n-butyl)picramide (**7**) in equilibrium with a very small amount of the anion (**8**). At higher amine:TNA ratios, further attack on the product (**7**) occurs giving (**9**) and the observed spectral changes are in agreement with the reactions in Scheme 2 where again the two-step mechanism for the substitution is clearly applicable. In the reaction of (**5**) with secondary amines at low temperatures it is thought that σ-complexes analogous to (**6**) are formed, but that substitution does not occur as the overall reaction, but rather as a side reaction to form the 1,1-dimethoxy Meisenheimer complex.



Scheme 2

Of the two systems studied, the reactions of (**5**) are better suited to n.m.r. investigations because of the simplicity of the spectra.

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[1] C. F. Bernasconi, MTP Internat. Rev. Sci. Org. Chem., Series one, 1973, **3**, 33—63, ed. H. Zollinger, Butterworths, London.

[2] J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1971, **49**, 275.

[3] (a) R. Foster and C. A. Fyfe, *Rev. Pure. Appl. Chem.*, 1966, **16**, 61; (b) M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7**, 211; (c) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev.*, 1968, **22**, 123; (d) M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667; (e) C. A. Fyfe in 'The Chemistry of the Hydroxyl Group,' Ed. S. Patai, Interscience, London, 1971.

[4] J. F. Bunnett and J. A. Orvik, *J. Amer. Chem. Soc.*, 1970, **92**, 2417.

[5] S. Sekiguchi, K. Shinozaki, T. Hirose, K. Matsui, and K. Sekine, *Bull.Chem. Soc. Japan*, 1974, **49**, 2264; S. Sekiguchi, T. Itageki, T. Hirose, K. Matsui, and K. Sekine, *Tetrahedron*, 1973, **29**, 3527.

[6] S. W. H. Damji, PhD Thesis, University of Guelph, 1975; C. A. Fyfe, M. Cocivera, and S. W. H. Damji, *J. Magnetic Resonance*, 1976, **23**, 377.

[7] C. A. Fyfe, M. Cocivera, and S. W. H. Damji, *J.C.S. Chem. Comm.*, 1973, 743; C. A. Fyfe, M. Cocivera, and S. W. H. Damji, *J. Amer. Chem. Soc.*, 1975, **97**, 5707; M. Cocivera, C. A. Fyfe, H. E. Chen, and S. P. Vaish, *J. Amer. Chem. Soc.*, 1974, **96**, 1611; M. Cocivera, C. A. Fyfe, H. E. Chen, S. P. Vaish, and A. Effio, *J. Amer. Chem. Soc.*, 1975, **97**, 5707; C. A. Fyfe, C. D. Malkiewich, S. W. H. Damji, and A. R. Norris, *J. Amer. Chem. Soc.*, 1976, **98**, 6983.