

Products and Mechanisms of the Reactions of Methyl 4-Nitrobenzyl Ether with *N*-Bromosuccinimide, *N*-Bromotetramethylsuccinimide and the *N*-Bromotetramethylsuccinimide–Tetrabutylammonium Tetramethylsuccinimide Complex

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The reactions of methyl 4-nitrobenzyl ether with *N*-bromosuccinimide, *N*-bromotetramethylsuccinimide and the *N*-bromotetramethylsuccinimide–tetrabutylammonium tetramethylsuccinimide complex have been studied. The formation of imido-substituted ethers with all three reagents is attributed to ionic mechanisms.

In the case of the complex, the mechanism involves base-catalyzed bromination of the substrate followed by nucleophilic substitution by the tetramethylsuccinimide anion. Imido substitution by *N*-bromoimides alone seems to be limited to substrates, RH, which correspond to stable carbocations, R⁺, such as α-oxy- and α-aza-carbocations, trityl cation and tropylium ion.

An electron-transfer (ET) mechanism was originally postulated to rationalize the decomposition of the *N*-bromosuccinimide–tetrabutylammonium succinimide complex (SBr–Bu₄N⁺S[–], where S = succinimidyl) in acetonitrile to give succinimide and polymaleimide.¹ However, the failure of the succinimidyl radical, S[•] a postulated intermediate of this mechanism, to exhibit many of the reaction modes attributed to S[•], (e.g. ring opening, substitution on aromatic rings, attack upon aliphatic double bonds, etc.)² raised doubt about the validity of this ET mechanism.

To test further the ET mechanism, the decomposition of the *N*-bromotetramethylsuccinimide–tetrabutylammonium tetramethylsuccinimide complex (TBr–Bu₄N⁺T[–]) in acetonitrile was studied. Since this complex lacks easily abstractable α-hydrogens, and disproportionation of 2 S[•] was assumed to be the pathway to maleimide from the SBr–Bu₄NS complex, we anticipated that tetramethylsuccinimide, TH, would be virtually the only product formed. However, in addition to TH, the experiment gave the totally unexpected product, tris(tetramethylsuccinimido)acetonitrile, T₃CCN,³ a result which led us to propose a polar

mechanism, which has now received extensive experimental support.⁴

In reactions with the complexes, both the *N*-bromoimide and the imide anion are available [eqn. (1); the equilibrium constant of (1) was determined to be ca. 10^{–4} M by a kinetic method⁴]. The reactions lead to substitution of hydrogen by an imido group at an acidic C–H, and the mechanism can be represented⁴ by the sequence of reactions (2)–(4), where (3) is an X-philic reaction.⁵



There are, however, many known reactions where substitution of an acidic α-H by a succinimido group can be effected by *N*-bromosuccinimide alone, without the addition of the succinimide anion, either as salt or as part of a complex with SBr. These include the reactions with 1,3,5-cycloheptatriene,⁶ methyl 4-nitrobenzyl ether,⁷ benzyl 4-

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bromophenyl ether,⁸ 1,3-dioxolanes,⁹ *N,N*-dimethylamido and *N,N*-dimethylamino groups¹⁰ and certain organic metal complexes.¹¹ Both purely free-radical mechanisms⁸ and mixed radical-ionic mechanisms^{9,10} have been proposed to account for these succinimido substitution reactions. These are of special interest because the initial reaction system does not contain a base to initiate the substitution process by removing a proton from the substrate [eqn. (2)]. If the substitution occurs by an ionic process it must involve some step or steps different from the reaction sequence of eqns. (2)–(4). To explore this possibility we have studied the reactions of methyl 4-nitrobenzyl ether with SBr, TBr and the TBr–T⁺Bu₄N⁺ complex.

Results and discussion

The reaction of methyl 4-nitrobenzyl ether with SBr to form *crude N*-(α -methoxy-4-nitrobenzyl)succinimide (**1**) in 29% yield was first described by Markees.⁷ When we repeated the reaction, using equimolar quantities of the ether and SBr in carbon tetrachloride we obtained a 10% yield of the purified product, **1**. By running the reaction with the ether and SBr at an initial molar ratio of 1:2 and modifying the procedure (see the Experimental) we were able to raise the yield of isolated purified product to 19% with carbon tetrachloride as the solvent and to 65% using acetonitrile as the solvent.

When this procedure was applied to the reaction between methyl 4-nitrobenzyl ether and TBr the product that resulted was not pure *N*-(α -methoxy-4-nitrobenzyl)tetramethylsuccinimide (**2**) but a mixture containing 4-nitrobenzaldehyde and **2** that was not separable by crystallization. The desired product, **2**, was separated from the 4-nitrobenzaldehyde by column chromatography on alumina (see the Experimental), and this made it possible to determine product compositions in the reactions of interest by GLC.

The reaction between methyl 4-nitrobenzyl ether and TBr was run in three solvents, carbon tetrachloride, dichloromethane and acetonitrile, using equimolar concentrations of the two starting reagents. In carbon tetrachloride the product yields (GLC) were 79% TH, 16% **2** and 79% 4-nitrobenzaldehyde. In dichloromethane the products were 92% TH, 0.7% **2** and 90% 4-nitrobenzaldehyde. In acetonitrile the products were 77% TH and 47% 4-nitrobenzaldehyde, and **2** was not obtained. The reaction in acetonitrile was also run using two equivalents of TBr per equivalent of methyl 4-nitrobenzyl ether. The products observed were 72% TH and 84% 4-nitrobenzaldehyde. Once again **2** was not a product.

The preferential formation of the aldehyde in the above reactions was unexpected. Its formation cannot be rationalized as arising from the hydrolysis of α -methoxy-4-nitrobenzyl bromide (**3**) by adventitiously introduced water. The solvents were reagent grade chemicals, and the reactions were protected from atmospheric moisture. A Karl Fischer titration of the acetonitrile used indicated that the

solvent contained only 12% of the water that would be required to account for the amount of 4-nitrobenzaldehyde formed. The sequence of reactions (5)–(7), where (7) is a displacement reaction by bromide ion on the methyl group, represents a possible rationalization of the observed results. Steric hindrance, introduced by the four methyl groups in the tetramethylsuccinimide moiety, may also play a role by inhibiting the formation of **2** and hence favoring reaction (7).



Ar = 4-nitrophenyl

A series of experiments was run in which ca. 0.0030 mol of methyl 4-nitrobenzyl ether and ca. 0.0015 mol of the *N*-bromotetramethylsuccinimide–tetramethylsuccinimide ion complex (hereafter referred to as the T complex) in 5 ml of solvent were refluxed for 15–20 h, and the products formed were then determined by gas chromatography. In these experiments the maximum concentration of TH that can form is twice that of the T complex, while the maximum concentration of the substitution product, **2**, that can be obtained is equal to the T complex concentration. The results obtained in three solvents are summarized in Table 1. In dichloromethane the tetramethylsuccinimide anion reacts preferentially with the solvent, and the major product is bis(tetramethylsuccinimido)methane (**4**) formed in 70% yield.

The facile formation of **4** in dichloromethane points to the pivotal role played by the anion and adds additional support to the polar reaction mechanism indicated by the reaction sequence (2)–(4).⁴ The reactions with the T complex do not exhibit reaction characteristics typical of a radical chain process. However, in the reactions of SBr and TBr, where the anion, S[–] or T[–], is absent at least initially, radical chain characteristics are apparent, and the reaction is accompanied by the formation of bromine and some evolution of hydrogen bromide. The first step is a Wohl–

Table 1. Products in the reaction of methyl 4-nitrobenzyl ether with the T complex.

Solvent	Yield of TH/%	Yield of 2 /%
CCl ₄	51.7	27.7
Benzene	55.3	35.1
CH ₂ Cl ₂ ^a	56.0	1.4
CH ₃ CN	60.5	27.4

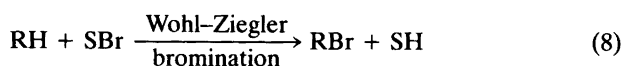
^aThe major product in dichloromethane is bis(tetramethylsuccinimido)methane (**4**) formed in 70% yield.

Ziegler reaction¹² which converts methyl 4-nitrobenzyl ether into the bromide **3**. However, the subsequent steps, which convert **3** into a succinimido-substituted derivative are polar, rather than free radical, in nature.

The first indication of polar reaction characteristics came from the reaction of methyl 4-nitrobenzyl ether and SBr, where a change from a non-polar solvent, carbon tetrachloride, to a polar solvent, acetonitrile, increased the yield of **1** from 19 to 65%. Further support comes from the chemical nature of the substrates, RH, which can be converted into succinimido derivatives and those which are not substituted by the succinimido group.

When 4-nitrotoluene in carbon tetrachloride was allowed to react for 6 h with an equimolar quantity of SBr the only products obtained were succinimide and 4-nitrobenzyl bromide. When the same reaction was run for 31 h with two mole equivalents of SBr and acetonitrile as the solvent, the only substitution product obtained was still 4-nitrobenzyl bromide. Diphenylmethane, treated similarly, also failed to give any succinimido substitution product.

In contrast, triphenylmethane reacted with two equivalents of SBr in carbon tetrachloride to give a 74% yield of *N*-tritylsuccinimide (**5**). This positive result is not surprising since Schreiber and Fernandez¹³ have shown that trityl bromide and SBr in equimolar quantities refluxed for 3–4 h in dry chloroform results in a 67% yield of **5**. In view of the foregoing discussion it is logical to postulate trityl bromide as an intermediate in the reaction of triphenylmethane and SBr. The sequence of reactions of eqns. (8)–(11) represents a reasonable reaction mechanism for compounds RH, the corresponding carbocations of which, R⁺, are relatively stable.



Here eqn. (8) is a standard Wohl-Ziegler side-chain bromination¹² and eqn. (10) is an X-philic reaction.⁵ The crucial step is the equilibrium shown in eqn. (9). The succinimido replacement will occur only in systems where this equilibrium is far enough to the right to supply a sufficient concentration of bromide ion to permit the X-philic reaction, eqn. (10). With both methyl 4-nitrobenzyl ether and triphenylmethane this requirement is met, but with 4-nitrotoluene and diphenylmethane as substrates the equilibrium in eqn. (9) is too far to the left.¹⁴

Conclusions

Apart from the conventional free-radical bromination reaction (Wohl-Ziegler bromination), *N*-bromoimides can be used to effect imido substitution according to two mechanisms, both exemplified above with methyl 4-nitrobenzyl ether. One is a base-catalyzed process [eqns. (1)–(4)], which can be employed for substrates containing enolizable hydrogens,⁴ whereas the second [eqns. (8)–(11)] applies to compounds RH which correspond to stable carbocations, R⁺. Several previous examples of the latter mechanism have been published^{6–10} and we draw attention to these studies which support the generality of the Scheme of eqns. (8)–(11). We are convinced that there will be possible synthetic applications of both mechanisms.

Experimental

The preparation of *N*-bromotetramethylsuccinimide has been described,¹⁵ as have the preparations of the *N*-bromotetramethylsuccinimide-tetrabutylammonium tetramethylsuccinimide complex⁴ and methylenebis(*N,N*-tetramethylsuccinimide).⁴

Methyl 4-nitrobenzyl ether. Sodium (4.7 g, 0.204 mol) was reacted with methanol (400 ml). 4-Nitrobenzyl bromide (44.0 g, 0.204 mol) was added, and the solution was refluxed for 6 h where upon. The reaction mixture was taken to dryness with a water pump. The residue was taken up in 500 ml of water and extracted four times with 500 ml portions of dichloromethane. The dichloromethane extract was dried over anhydrous magnesium sulfate. The mixture was filtered, and the solution was distilled at the water pump. The product, obtained in 70% yield, boiled at 133–138°C/10–12 mmHg.

N-(α-Methoxy-4-nitrobenzyl)succinimide (1). The reaction in acetonitrile is typical of our modified procedure. Methyl 4-nitrobenzyl ether (1.00 g, 0.00598 mol) and *N*-bromosuccinimide (2.15 g, 0.0121 mol) in solution in acetonitrile (10 ml) were left to stand overnight at room temperature and then refluxed for 2 h. The reaction mixture was taken up in dichloromethane (150 ml) and extracted with 2×50 ml of 10% sodium hydroxide. The aqueous layers were back-extracted with 50 ml of dichloromethane, and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was filtered, the solvent was removed with the water pump, and the crude product was crystallized from ethanol. The yield was 1.03 g (65%), m.p. 148–150°C. The same quantities of starting materials refluxed for 4 h in carbon tetrachloride and worked up as above gave a 19% yield of the product.

When a solution of 4-nitrobenzyl methyl ether (1.00 g, 0.00598 mol) and SBr (1.0 g, 0.00598 mol) in carbon tetrachloride (10 ml) was refluxed for 4 h and then made up to 50 ml with acetonitrile for GLC analysis, the products found were 84% succinimide and 16% **1**.

N-(α -Methoxy-4-nitrobenzyl)tetramethylsuccinimide (**2**). Methyl 4-nitrobenzyl ether (2.01 g, 0.01202 mol) and *N*-bromotetramethylsuccinimide (2.80 g, 0.01196 mol) in carbon tetrachloride (20 ml) were refluxed for 4 h. The reaction mixture was taken up in a mixture of benzene (100 ml) and ether (100 ml). It was extracted with 4×50 ml of 15 % sodium hydroxide solution, and the aqueous extracts were back-extracted with ether (150 ml). The combined organic layers were dried over magnesium sulfate. The solution was filtered and taken to dryness with the water pump. The crude product was crystallized from ethyl acetate-hexane (1.56 g), m.p. 84–92 °C. The ¹H and ¹³C NMR spectra of this product indicated that it was a mixture of 4-nitrobenzaldehyde and **2**, which we were unable to separate by recrystallization.

To separate **2**, a solution of 0.518 g of the above product in 50 ml of carbon tetrachloride was subjected to chromatography on a 2.5×27 cm column of alumina. Two 50 ml portions of carbon tetrachloride were used for elution, and small fractions were taken from the column and checked for the presence of the product. When the first three fractions gave no product on evaporation of the solvent, the elution solvent was changed to 4 % acetone/96 % carbon tetrachloride (v/v). Two more fractions taken from the column gave no product on evaporation, but the sixth fraction gave a small amount of white solid, m.p. 132–141 °C. The seventh fraction contained all of the product: 166 mg, m.p. 148–149 °C. Anal. C₁₆H₂₀N₂O₅: C, H, N.

Once an authentic sample of **2** was available it became possible to determine by GLC the products formed in the reaction of methyl 4-nitrobenzyl ether with both TBr and the T complex. The reaction with TBr was run in both carbon tetrachloride and dichloromethane. In a typical experiment, 0.006 mol of the ether and 0.006 mol of TBr in 10 ml of either CH₂Cl₂ or CCl₄, were refluxed for 3–5 h and then made up to 50 ml with acetonitrile for GLC analysis. The reactions with the T complex have been discussed in the Results and Discussion section.

Reaction of triphenylmethane and N-bromosuccinimide. Preparation of N-tritylsuccinimide. Triphenylmethane (3.44 g, 0.01 mol) and *N*-bromosuccinimide (3.56 g, 0.02 mol) in CCl₄ (50 ml) were refluxed for 20 h. The reaction mixture was taken up in 100 ml of chloroform and extracted with 2×50 ml of 10 % sodium hydroxide solution. The aqueous layers were back-extracted with 75 ml of chloroform. The organic extracts were dried over magnesium sulfate. After filtration and removal of the solvent with the water pump, the crude product was crystallized from acetone-hexane:

yield 2.46 g (75 %), m.p. 204–209 °C. Anal. C₂₃H₁₉NO₂: C, H, N. A small sample recrystallized from acetone-hexane had m.p. 205–208 °C.

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References

1. Barry, J. E., Finkelstein, M., Moore, W. M., Ross, S. D. and Ebersson, L. *Tetrahedron Lett.* 25 (1984) 2847.
2. For reviews see, Lüning, U. and Skell, P. S. *Tetrahedron* 41 (1985) 4289; Chow, Y. L. and Naguib, Y. M. A. *Rev. Chem. Intermediat.* 5 (1984) 325.
3. Finkelstein, M., Hart, S. A., Ross, S. D. and Ebersson, L. *Acta Chem. Scand., Ser. B* 41 (1987) 232.
4. Ebersson, L., Lepistö, M., Finkelstein, M., Hart, S. A., Moore, W. M. and Ross, S. D. *Acta Chem. Scand., Ser. B* 42 (1988) 666.
5. Zefirov, N. S. and Makhonkov, D. I. *Chem. Rev.* 82 (1982) 615.
6. Dryden, H. L., Jr. and Burgert, B. E. *J. Am. Chem. Soc.* 77 (1955) 5633.
7. Markees, D. G. *J. Org. Chem.* 23 (1958) 1490.
8. Braun, L. L. and Looker, J. H. *J. Org. Chem.* 26 (1961) 574.
9. Bazbouz, A., Christol, H., Coste, J., Pietrasanta, F. and Plenat, F. *Tetrahedron* 36 (1980) 2757.
10. Caristi, C., Ferlazzo, A. and Gattuso, M. *J. Chem. Soc., Perkin Trans. I* (1984) 281.
11. Nagahara, T., Kasuga, K. and Yamamoto, Y. *Inorg. Nucl. Chem. Lett.* 17 (1981) 235; Gordetsov, A. S., Pereshin, V. V., Konkina, T. N., Lityaeva, V. N., Dergunov, Yu. I. *J. Gen. Chem. (Engl. Transl.)* 53 (1983) 1511.
12. Djerassi, C. *Chem. Rev.* 43 (1948) 271; Waugh, T. D. *NBS, Its Reactions and Uses*, Arapahoe Chemicals, Boulder, Colo., 1951.
13. Schreiber, K. C. and Fernandez, V. P. *J. Org. Chem.* 26 (1961) 1744.
14. These results are more credible when one notes that at 25 °C in 40 % ethanol-60 % diethyl ether, the alcoholysis of trityl chloride is four orders of magnitude faster than the alcoholysis of benzhydryl chloride. Nixon, A. C. and Branch, G. E. *K. J. Am. Chem. Soc.* 58 (1936) 492.
15. Bickel, A. F. and Waters, W. A. *Recl. Trav. Chim.* 69 (1950) 1490; Pearson, R. E. and Martin, J. C. *J. Am. Chem. Soc.* 85 (1963) 3142.

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