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Regiochemical variation in the electrophilic addition of HBr to 1-phenylprop-1-yne

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The reaction of aryl alkynes with dilute methylene chloride solutions of quaternary ammonium bromide and 20% trifluoroacetic acid produces primarily the *syn* Markovnikov adducts of hydrogen bromide. At moderate concentrations of the bromide, the principal product is the Markovnikov *anti* adduct. At high concentrations of bromide, the anti-Markovnikov *anti* addition product predominates.

Introduction

In a previous paper,[1] we showed that the electrophilic addition of HBr to unconjugated alkynes proceeds *via* an Ad_E3 mechanism where the bromide ion attacks an acid–alkyne complex in the rate determining step. Thus, the rate was bromide dependent and the initial products resulted from an *anti* addition.

Fahey *et al.* had reported[2] that 1-phenylprop-1-yne adds to HCl (in acetic acid) by a competition between this concerted mechanism and an Ad_E2 process involving a vinyl cation conjugated with the aryl ring. The latter cationic intermediate was also postulated[3] in the acid catalyzed hydration of aryl alkynes which showed a kinetic dependence on the σ^+ value for the substituted aryl alkynes. The *p*-methoxyphenyl vinyl cation has also been seen[4] by NMR at −80 °C.

We initiated this study to look at these reactions more fully under the conditions of our previous work in which we were able to vary the acidity of the solutions and the concentrations of the relatively nucleophilic bromide ion. The unconjugated alkynes were reacted with a large excess of 20% trifluoroacetic acid in methylene chloride containing variable, excess amounts of tetra-*n*-butylammonium bromide. Low concentrations of bromide ion were seen to increase the acidity of these trifluoroacetic acid solutions whereas higher concentrations of bromide decreased the acidities as measured[5] by their abilities to protonate a Hammett base.[1] It should be noted that part of the acid-weakening effect of the concentrated salt solutions derives from the dilution of the acid by large volumes of salt. In a 2.0 molar solution of bromide, the concentration of the "20%" trifluoroacetic acid is only 8%. Over this range, the H_o-pK_a value was found to rise only 0.04 units for each one percent drop in the concentration of trifluoroacetic acid when diluted by solvent. By contrast, the dilution of a 20% trifluoroacetic acid solution by the quaternary ammonium salt to a 12% TFA solution spans more than four H_o units.[5] The simple TFA dilution factor is therefore seen to be insignificant.

Results and discussion

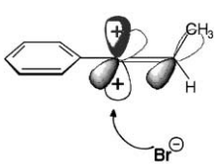
Product studies

Our initial studies looked at the addition of HBr to 1-phenylprop-1-yne as this substrate could provide data on the regioselectivity and stereoselectivity of the reaction. Three products were found (Scheme 1) and these results are reported in Table 1.

Table 1 Fractions of HBr addition products at each concentration of tetrabutylammonium bromide

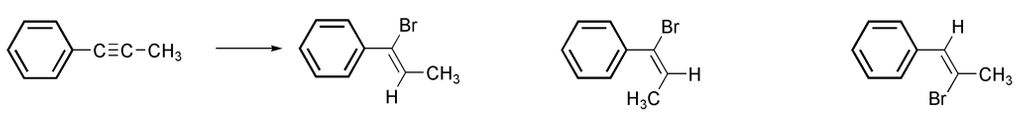
[Bromide]	E1B	Z1B	Z2B
0.050	0.794	0.206	0.000
0.101	0.795	0.205	0.000
0.209	0.777	0.223	0.000
0.397	0.735	0.265	0.001
0.597	0.631	0.366	0.003
0.815	0.301	0.618	0.081
0.983	0.067	0.668	0.265
1.100	0.020	0.619	0.361
1.244	0.000	0.527	0.473
1.300	0.000	0.465	0.535
1.399	0.000	0.418	0.582
1.600	0.000	0.321	0.679
1.995	0.000	0.153	0.847

At the lowest concentration of bromide (0.05 M), the principal product was the (*E*)-1-bromo-1-phenylprop-1-ene (**E1B**). This is good evidence for the intermediacy of a free vinyl cation which is primarily attacked by bromide on the sterically less hindered side (Scheme 2). This four to one preference for the *syn* adduct is repeated at double the bromide concentration and is changed little at a tenfold increase of bromide ion. We can assume that this ratio of products is a result of the cationic mechanism operating in solutions of high acidity and low bromide concentration. Above a 0.4 molar concentration of bromide ion, we begin to find the anti-Markovnikov product, (*Z*)-2-bromo-1-phenylprop-1-ene (**Z2B**) being formed, presumably by a concerted Ad3 mechanism.† The decreasing acidity slows the independent protonation of the alkyne while the increasing bromide concentration also promotes its attack on



Scheme 2

† The increasingly important role of the nucleophile in these reactions has prompted us (as well as Fahey and co-workers) to drop the "E" from the Ad_E3 descriptor for this mechanism.



PPy Z1B E1B Z2B

Scheme 1

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the acid–alkyne complex. At the same time, the proportions of *anti* added Markovnikov product (**Z1B**) increases as a result of the antiperiplanar bromide attack on the acid–alkyne complex. If we assume a constant 4 : 1 ratio of Markovnikov products from the Ad_E2 mechanism, we can partition the fraction of reaction occurring by each route (Fig. 1a and 1b). We can use this to partition the pseudo-first order rate constants into rate constants for each mechanism.

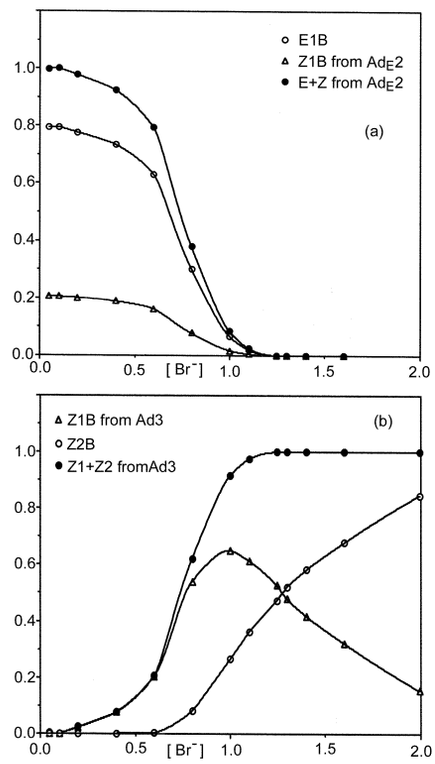

Fig. 1 (a) Fraction of products coming from the Ad_E2 route *vs.* bromide concentration. (b) Fraction of products coming from the Ad3 route *vs.* bromide concentration.

As the concentration of bromide ion in the reaction medium increases, the acidity decreases, the Ad_E2 reaction slows significantly and the concerted mechanism produces an increasing fraction of the products. The Markovnikov adduct (**Z1B**) predominates at the mid-range concentrations of bromide but as the solution becomes even less acidic (above 1.3 M bromide), the anti-Markovnikov adduct (**Z2B**) becomes the major product. We initially believed that the increasing bromide concentration weakening the acidity of the reaction medium caused the transition state to develop less cationic character and, therefore, less preference for the Markovnikov product. However, this explanation fell short of explaining the continuation of the trend to the point of favoring the anti-Markovnikov product in the most concentrated bromide solutions.

Fahey *et al.*[2] found a similar distribution pattern of the corresponding chloride products in the addition of HCl (in acetic acid) to 1-phenylprop-1-yne. With no added chloride, the *syn* Markovnikov adduct predominated. Added tetramethylammonium chloride increased the proportion of the *anti* adduct and also produced a small amount of the (*Z*)-2-chloro-1-phenylprop-1-ene. This anti-Markovnikov product rose to 16% of the chloride *anti*-addition adducts at the maximum chloride concentration (1.0 molar) but never became predominant. As in our studies, the anti-Markovnikov (*E*) isomer was never observed. Unlike our results, the increased chloride ion concentrations increased the rates of these reactions as it had less of an acid-weakening effect in the acetic acid solvent. With those results in hand, Fahey was comfortable postulating a competition between the Ad_E2 and Ad3 mechanisms.

Table 2 Rate constants ($min^{-1} \times 10^{-3}$) for each mechanism and total

[Bromide]	*k* (PPy + Br)	*k* (Ad_E2)	*k* (Ad3)
0.050	481	481	0.000
0.101	347	347	0.000
0.209	385	377	8.25
0.397	100	93.0	7.47
0.597	23.1	18.4	4.74
0.815	0.924	0.350	0.574
0.983	0.139	0.012	0.127
1.100	0.091	0.002	0.089
1.244	0.041	0.000	0.041
1.300	0.044	0.000	0.044
1.399	0.028	0.000	0.028
1.600	0.009	0.000	0.009

Kinetic studies

In our previous studies,[1,5] we showed that the pseudo-first order rate constants for the addition of HBr to alkynes divided by the concentrations of bromide for these additions were linearly proportional to the pseudo-first order rate constants for the addition of HBr to the corresponding alkenes under the same conditions. This was strong kinetic evidence that alkenes react by the Ad_E2 mechanism while alkynes use the Ad3 route including the bromide ion in the rate determining step. The rate constants for the addition of HBr to 1-phenylprop-1-yne are shown in Table 2 along with the rate constants for each mechanism calculated from the partitioning of the products.

When we plot the logarithm of the rate constants for the HBr addition to 1-phenylprop-1-yne against the logarithm of the rate constants for the Ad_E2 addition to oct-1-ene under the same conditions (Fig. 2a), we see clear curvature. When we plot the logarithm of the calculated pseudo-first order rate constants for the Ad_E2 portion of this reaction against the log of the pseudo-first order rate constants for the HBr addition to

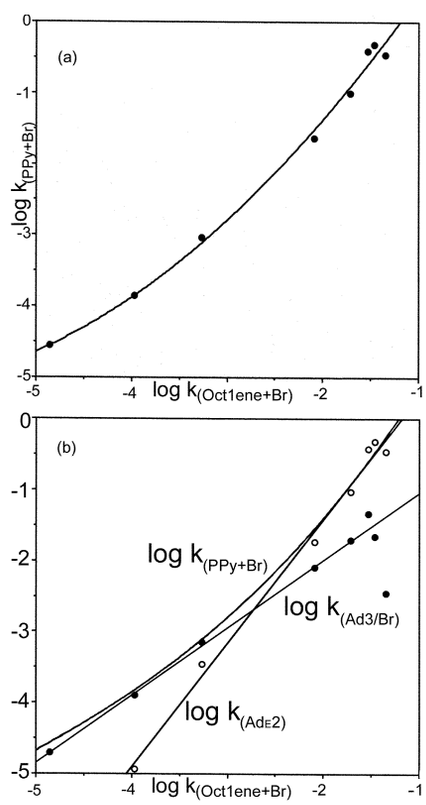

Fig. 2 (a) Logarithm of pseudo-first order rate constants for the HBr addition to 1-phenylprop-1-yne *vs.* HBr addition to oct-1-ene. (b) Logarithm of pseudo-first order rate constants for Ad_E2 (○) and Ad3 (●) contributions to the HBr addition to 1-phenylprop-1-yne *vs.* HBr addition to oct-1-ene (Log k_{total} is included for comparison).

oct-1-ene (Ad_E2 behavior) we find a linear relationship fitting the overall rate curve at the lower concentrations of bromide (Fig. 2b). Similarly, if we plot our calculated pseudo-first order rate constants for the Ad3 portion *divided by the bromide concentrations* of the solutions in which the reactions were performed *versus* the rate constants for the HBr additions to oct-1-ene, we find a good linear relationship (with one outlying data point) fitting the overall rate at the higher concentrations of bromide. This supports Fahey's idea that the Ad_E2 mechanism predominates at low bromide concentrations but that increased bromide causes the Ad3 mechanism to be favored.

Effect of acid concentration

Recognizing that the 20% trifluoroacetic acid is diluted to an 8% acid solution by the addition of the quaternary ammonium bromide to make it 2.0 M in salt, we sought to see whether similar results might be found with a weak acid solution prepared with less acid and less salt. A 1.0 M salt solution was made with 5% trifluoroacetic acid in methylene chloride giving a final concentration of 3.5% trifluoroacetic acid. The 1-phenylprop-1-yne was found to react very slowly in this medium but to produce 80% anti-Markovnikov addition; regioselectivity quite similar to the 2.0 M salt using 20% trifluoroacetic acid. The regioselectivity is therefore seen to be primarily a result of the acidity of the solution.

Effect of solvent polarity

Since methylene chloride has a relatively high dipole moment (1.6 D) and dielectric constant (8.9), we substituted carbon tetrachloride (0.0 D and 2.2) in various proportions. Even the total replacement of CH_2Cl_2 by CCl_4 had little effect on the rates or product distributions. We had hoped that the less polar solvent might promote an increase in the Ad3 anti-Markovnikov product.

Effect of anion nucleophilicity

We wanted to examine the behavior of the iodide ion in solutions of the same acidity but we found it impossible to determine the H_o of iodide solutions due to the unavoidable oxidation of iodide. To circumvent this problem, we used a solution which was 0.8 M in bromide and in iodide and compared the relative production of isomers from each anion. Under these conditions, the anti-Markovnikov adduct comprised 44% of the vinyl iodides while it accounted for 39% of the bromide adducts. Although the more nucleophilic iodide ion produced 90% of the hydrogen halide adducts, the regioselectivity from both anions was not significantly different. This result suggests that the nucleophiles are involved in the rate and product determining steps leading to *both* Markovnikov and anti-Markovnikov products from both anions. The more nucleophilic iodide must be increasing the rate of formation of both vinyl iodides to maintain their ratio so close to the ratio of vinyl bromides. Therefore all products are being formed by Ad3 mechanisms. The explanation for this result only became clear after the extensive studies described in our next paper.

Conclusion

In strongly acidic solutions, conjugated aryl alkynes containing low concentrations of bromide ion, undergo protonation to form resonance stabilized vinyl cations. In less acidic solutions containing higher concentrations of a good nucleophile, a concerted mechanism becomes dominant in which the nucleophile can attack the acid–alkyne complex. The less polarized transition state for this concerted mechanism causes an increased proportion of anti-Markovnikov product. At the highest concentrations of bromide ion, the anti-Markovnikov product predominates. The reason for this will be addressed in the subsequent paper.

Table 3 GC and NMR data on HBr adducts from 1-phenylprop-1-yne.

Product	GC%	NMR vinyl protons		NMR methyl protons	
E1B	3.4%	64.5%	6.24 ppm (q)	5%	1.64 ppm (d)
Z1B	61.2%		6.24 ppm (q)	57%	1.93 ppm (d)
Z2B	35.5%	35.5%	6.68 ppm (s)	38%	2.48 ppm (s)

Experimental

The 1-phenylprop-1-yne, trifluoroacetic acid and solvents (HPLC grade) used in these experiments were obtained from Aldrich Chemical Co. and were used without further purification. The 1-phenylprop-1-yne was also obtained from GFS Chemicals. The quaternary ammonium salts were obtained from Fluka Chemical and from Aldrich Chemical Co. and were kept in a desiccator prior to use. The tetrabutylammonium bromide was dried under vacuum at regular intervals.

Reactions were performed in glass-stoppered volumetric flasks by adding 1 or‡ 2 drops of the alkyne§ to 5–100 mL¶ of the 20% trifluoroacetic acid in methylene chloride solution containing the quaternary ammonium salt. Aliquots (approximately 0.5 mL) were removed and quenched with 15 mL of water and 10 mL of hexanes. The hexane layer was washed with another 15 mL of water and dried over anhydrous potassium carbonate prior to GC-MS analysis. Chromatographic peaks were identified by their mass spectrum as well as by a comparison of a mixture analyzed by NMR. Relative detector responses for the isomeric vinyl bromides were assumed to be equal and this was supported by the similar quantitative results obtained from the NMR analysis (*vide supra*). The vinyl bromides were shown to be stable under the reaction conditions in spite of a slow addition of a second molecule of HBr. Unless otherwise noted, all reactions were run at room temperature (20 ± 2 °C) and showed no evidence of exothermicity.

A preparative scale reaction on 1-phenylprop-1-yne was analyzed by GC-MS and by NMR. The NMR spectrum showed overlapping quartets for the vinyl protons of the Markovnikov adducts but the methyl proton signals were well resolved. These data are collated in Table 3. The mass spectra of the Markovnikov adducts were virtually identical while the anti-Markovnikov adduct gave a significantly stronger molecular ion (196, 198).

NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer utilizing a deuterium lock and TMS as internal reference. Mass spectra and chromatographic analyses were performed on a Hewlett Packard 5890 Chromatograph with a 12 m, HP-1 capillary column and a 5971A mass selective detector.

Acknowledgements

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‡ Results from 1 or 2 drops of alkyne (approximately 10^{-4} moles) are identical within our experimental uncertainty.
§ In all kinetic studies, a preanalyzed mixture of alkyne and decane was used.
¶ At least 10^{-3} moles of bromide ion was used.

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