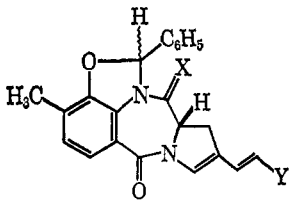

20, X = O; Y = CN
21, X = O; Y = $CONH_2$
22, X =  ; Y = $CONH_2$

pound **18** with *p*-toluenesulfonyl chloride in pyridine at 50° yielded the *trans*-nitrile **19** [17% over-all yield from **2**; δ^{DMSO} 5.58 ppm (1 H, doublet, J = 16 Hz)] which, when heated in boiling methanol in the presence of triethylamine, afforded the phenol **16** [98%; δ^{DMSO} 5.54 and 7.43 ppm (two 1 H doublets, J = 16 Hz)]. Condensation of the latter compound with benzaldehyde dimethyl acetal[13] at 200° under nitrogen gave the benzal derivative **20** [60%; mp 194–195° (*in vacuo*)] which was converted to the amide **21** [67%; mp 281–282° dec (*in vacuo*)] upon treatment with hot (95°) polyphosphoric acid followed by aqueous work-up.

Reduction of compound **21** with lithium aluminum hydride in tetrahydrofuran at −60° *or* with sodium borohydride in methanol at 5° (preferred method), followed by hydrolysis of the resulting carbinolamine **22** [δ^{DMSO} 4.85 (1 H, doublet, J = 9 Hz; singlet after exchange)[2]] with 0.01 *N* aqueous hydrochloric acid in methanol, afforded a 70% over-all yield of anthramycin methyl ether (**2**), identical in every respect (including microbiological activity) with an authentic sample.

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(13) E. Fischer and G. Giebe, *Chem. Ber.*, **31**, 545 (1898).

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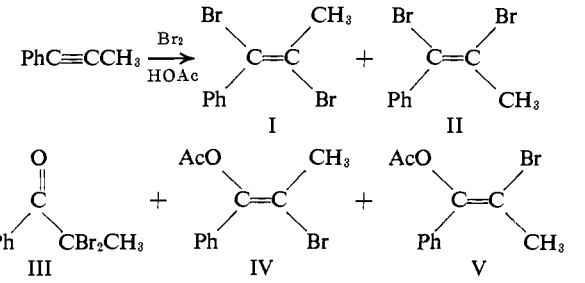
On the Mechanism of Bromination of Acetylenes

Sir:

Although the electrophilic addition of bromine to olefins has been extensively studied and the main details of the reaction are well understood,[1] very little is known about the mechanism of the corresponding reaction with acetylenes. The only kinetic work available is an early study by Robertson[2] on the bromination of a series of substituted acetylenes in acetic acid indicating that the reaction is an electrophilic addition and that the rate expression involves first- and second-order bromine terms similar to those observed for olefins. However, no systematic study of the products and stereochemistry in relation to the kinetics is available, and consequently we wish to report our preliminary results here.

The bromination of methylphenylacetylene in acetic acid yields five products: *trans*-1,2-dibromo-1-phenylpropene (I), *cis*-1,2-dibromo-1-phenylpropene (II), 1,1-dibromoethyl phenyl ketone (III), and *trans*- and *cis*-1-acetoxy-2-bromo-1-phenylpropenes (IV and V).



The products were isolated from the reaction mixture by extraction with pentane and separated by a combination of column and preparative-scale gas chromatography. The stereochemistry of I and II was established from their dipole moments, the *trans* isomer having a value of 0.1 D and the *cis* isomer a value of 2.2 D. The dibromo ketone III is identical with the product of an acid-catalyzed bromination of propiophenone and could also be obtained by the bromination of the mixture of IV and V in acetic acid. This establishes that III is a secondary reaction product and also that the bromoacetates are the 1-acetoxy compounds rather than the isomeric 2-acetoxy forms. The bromoacetates obtained could not be separated by vpc, but an nmr spectrum of the mixture indicated the two isomeric compounds were present in the ratio of 2.6:1. However, no assignment of their stereochemistry could be made on the basis of the nmr spectrum alone.

In control experiments under the reaction conditions no isomerization of the dibromides or reaction to give bromoacetates was observed. The results of product studies in pure acetic acid and in the presence of added salts are shown in Table I. Of particular interest is the

Table I. Products of Bromination of Methylphenylacetylene (MPA) in Acetic Acid at 25°

(MPA), 10^2 *M*	(Br_2), 10^3 *M*	Added salt, *M* LiBr	$LiClO_4$	Product composition, %[a] I	II	III	IV + V
3.34	3.78			59.2	13.7	6.1	21.0
8.85	4.56			55.5	12.4	13.9	18.1
10.3	10.3			59.4	13.9	8.9	17.7
10.1	5.82		0.10	47.8	10.3	15.2	26.6
7.90	3.96		0.10	53.3	9.6	12.9	24.1
3.37	3.78	0.10		98	0.2	0.5	1.5
3.77	3.78	0.06	0.04	98	0.2	0.5	1.5
3.56	3.78	0.02	0.08	92.5	1.0	2.0	4.5

[a] Evaluated by vpc from peak areas.

result that although the reaction is only selective in the pure solvent (*trans*:*cis* 4.2:1 for dibromide formation) it occurs with virtually 100% *trans* stereospecificity in the presence of lithium bromide. An interpretation of this result requires a knowledge of the kinetic processes occurring under the conditions studied.

The kinetics of the addition reaction follow the general equation

$$-\frac{d(Br_2)_T}{dt} = k_2(MPA)(Br_2) + k_3(MPA)(Br_2)^2 + k_{Br^-}(MPA)(Br_2)(Br^-) \quad (1)$$

where (MPA) is the concentration of methylphenyl-

(1) P. B. D. de la Mare and R. Bolton, "Electrophilic Addition to Unsaturated Systems," Elsevier Publishing Co., New York, N. Y., 1966, Chapter 7.
(2) P. W. Robertson, W. E. Dasent, R. M. Milburn, and W. H. Oliver, *J. Chem. Soc.*, 1628 (1950).

acetylene and $(Br_2)_T$ is the total bromine concentration. The third term in the expression is only included in the presence of added bromide ion. At low bromine concentrations the term second order in bromine becomes negligible, so that by studying the kinetics at initial bromine concentrations of less than 3×10^{-4} M (using 10-cm cuvettes in a Cary 16 spectrophotometer) k_2 can be evaluated. This value of k_2 was then used to obtain k_3 from kinetic runs at higher bromine concentrations. Values of the rate constants and their mean deviations for acetic acid at 24.8° are $k_2 = (2.46 \pm 0.06) \times 10^{-3}$ M^{-1} sec^{-1} and $k_3 = 2.7 \pm 0.3$ M^{-2} sec^{-1}.

In the presence of added bromide ion the formation of tribromide ion lowers the free bromine concentration so that the rate expression becomes

$$-\frac{d(Br_2)_T}{dt} = k_2(MPA)(Br_2) + k_{Br^-}(MPA)(Br_2)(Br^-) \quad (2)$$

but

$$-\frac{d(Br_2)_T}{dt} = k_{obsd}(MPA)(Br_2)_T \quad (3)$$

and

$$Br^- + Br_2 \rightleftharpoons Br_3^-$$

$$K = \frac{(Br_3^-)}{(Br_2)(Br^-)} \quad (4)$$

so that

$$(Br_2)_T = (Br_2) + (Br_3^-) \quad (5)$$

where k_{obsd} is the observed second-order rate constant and K is the tribromide equilibrium constant.[3] Solution of eq 2–5 gives eq 6, which makes it possible to

$$[1 + K(Br^-)]k_{obsd} = k_2 + k_{Br^-}(Br^-) \quad (6)$$

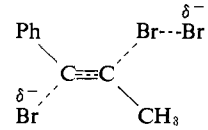
obtain the separated rate constants by studying k_{obsd} as a function of bromide ion concentration. Rates were followed by a potentiometric method[3] with LiBr concentrations from 0.02 to 0.10 M and ionic strength kept constant at 0.10 with added $LiClO_4$. A plot of $[1 + K(Br^-)]k_{obsd}$ *vs.* (Br^-) gives values of $k_2 = (8.1 \pm 7.6) \times 10^{-3}$ M^{-1} sec^{-1} and $k_{Br^-} = 2.88 \pm 0.03$ M^{-2} sec^{-1} from the intercept and slope of the least-squares line.

Equation 1 is kinetically indistinguishable from eq 7

$$-\frac{d(Br_2)_T}{dt} = k_2(MPA)(Br_2) + k_3(MPA)(Br_2)^2 + k_{Br_3^-}(MPA)(Br_3^-) \quad (7)$$

since the tribromide and bromide ion concentrations are related by the equilibrium shown in eq 4.[4] Therefore $k_{Br^-} = Kk_{Br_3^-}$. Equation 1 represents a bromide ion catalyzed attack of molecular bromine whereas eq 7 corresponds to a direct electrophilic attack by tribromide ion.[4] In the case of aromatic brominations, where no bromide ion catalysis is possible, tribromide ion terms have only been observed for the most reactive substrates.[5,6] For bromine additions to olefins, however, the results are not clear. Bell[7,8] has provided evidence that in aqueous solution, for a series of olefins covering a range of reactivity of 10^{10}, the tribromide ion process is occurring rather than the bromide ion catalyzed one, except for diethyl fumarate (the least reactive olefin studied). Kanyaev[9] has published results that disagree with Bell's and indicate that the process is a bromide ion catalyzed reaction for all cases. Our results for bromination of methylphenylacetylene in acetic acid strongly indicate that a bromide ion catalyzed process is most probable, at least for acetylenes. We believe this to be one of the few cases where a clear-cut decision can be made between these kinetically indistinguishable processes.

The ratio $k_{Br^-}(Br^-)/k_2$ is approximately 35 at 0.1 M lithium bromide, so that very little bromination by free bromine is occurring. The complete *trans* stereospecificity of dibromide formation and the dramatic decrease in bromoacetate formation under these conditions are consistent with a termolecular process (Ad_E3)[10] passing through a transition state like VI but would be very difficult to explain on the basis of attack



VI

by electrophilic tribromide ions. Such a direct electrophilic attack would be expected to give a similar intermediate cation and hence similar stereochemistry to that observed for the reaction with molecular bromine in the absence of added bromide ion.

Further work on substituted phenylacetylenes is in progress to study the relationship of the observed products to the various cationic intermediates that are possible for electrophilic additions in acetic acid.[11–13]

Acknowledgment. The continued financial support of the National Research Council of Canada and the award of a Studentship to J. A. P. are gratefully acknowledged.

(3) J. H. Rolston, Ph.D. Thesis, University of Toronto, 1967.
(4) Since lithium bromide is probably very little dissociated in acetic acid, both the Br^- and Br_3^- referred to in all these equations are present mainly as ion pairs.
(5) R. P. Bell and D. J. Rawlinson, *J. Chem. Soc.*, 63 (1961).
(6) J.-E. Dubois, P. Alcais, G. Barnier, and R. Uzan, *Bull. Soc. Chim. France*, 605, 611, 617 (1968).
(7) J. R. Atkinson and R. P. Bell, *J. Chem. Soc.*, 3260 (1963).
(8) R. P. Bell and M. Pring, *J. Chem. Soc., B*, 1119 (1966).
(9) N. P. Kanyaev, *J. Gen. Chem. USSR*, **29**, 825 (1959).
(10) R. C. Fahey and D.-J. Lee, *J. Am. Chem. Soc.*, **90**, 2127 (1968).
(11) M. L. Poutsma and J. L. Kartch, *ibid.*, **89**, 6595 (1967).
(12) R. C. Fahey and D.-J. Lee, *ibid.*, **88**, 5555 (1966).
(13) R. C. Fahey and D.-J. Lee, *ibid.*, **89**, 2780 (1967).

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The Addition of Halomethylene to 1,2-Dimethylcyclobutene, a Methylene–Olefin Reaction Involving a Novel Rearrangement[1]

Sir:

Recently we reported that photolyses of polyiodomethanes in neat cyclohexene led to the formation of norcaranes.[2] We suggested that the photolysis of a

(1) This work was supported by the U. S. Atomic Energy Commission Contract No. AT-(11-1)-1043. A preliminary account of this work was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, Abstracts, No. P73.
(2) T. Marolewski and N. C. Yang, *Chem. Commun.*, 1225 (1967). For related work, see D. C. Blomstrom, K. Herbig, and H. E. Simmons, *J. Org. Chem.*, **30**, 959 (1965); R. C. Neuman, Jr., and R. G. Wolcott, *Tetrahedron Letters*, 6267 (1966).