

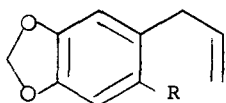
SOLVENT EFFECTS IN THE REACTION OF SAFROLE WITH BROMINE.<sup>1</sup>

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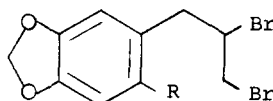
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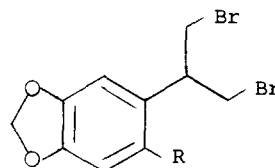
While the reaction of safrole (1a) with 1 mol of Br<sub>2</sub> in CHCl<sub>3</sub> gave ~65% of 2a along with ~35% of 3a<sup>2</sup>, a similar reaction of 1a with 2 moles of Br<sub>2</sub> without solvent gave ~55% of 2b together with ~45% of 3b,<sup>3</sup> suggesting that solvent effects could modify the outcome of this reaction. A study of these effects was undertaken and some of our preliminary results are shown in Table I.



1



2



3

a, R=H; b, R=Br

Based on the work of Dubois et al.,<sup>4</sup> we also propose that 2a and 3a arise from the reaction of a bromonium ion and a phenonium ion with bromide ion as shown in the following scheme:

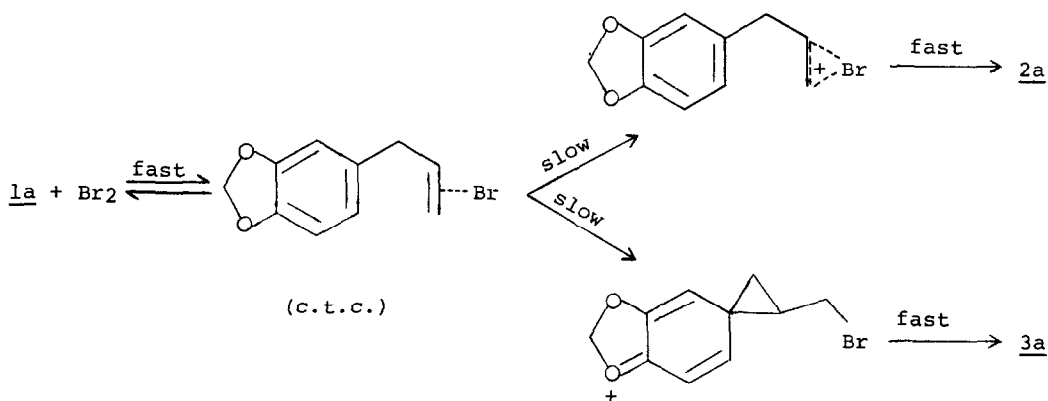


TABLE I. % Product Distribution in the Reaction of 1a with Br<sub>2</sub>.<sup>a</sup>

Solvent ( $\epsilon$ ) <sup>b</sup>	<u>2a</u> <sup>c</sup>	<u>3a</u> <sup>c</sup>	Initial Concentration of <u>1a</u> (M)x10 <sup>2</sup>	<u>3a/2a</u>
CCl <sub>4</sub> (2.23)	65.8	34.2	22.6	0.52
CHCl <sub>3</sub> (4.80)	64.6	35.4	22.6	0.55
	60.2	39.8	2.26	0.66
	52.4	47.6	0.56	0.99
CH <sub>2</sub> Cl <sub>2</sub> (8.93)	47.0	53.0	22.6	1.12
CH <sub>2</sub> ClCH <sub>2</sub> Cl (10.36)	32.5	67.5	22.6	2.08
	32.5	67.5	2.26	2.08
	32.5	67.5	0.56	2.08
t-BuOH (12.47)	>95%	<5%	22.6	-
MeOH <sup>d</sup> (32.70)	58.5	41.5	22.6	0.71
	36.4	63.6	2.26	1.75

- a) A solution of 1a (0.1 ml, ~0.68 mmoles) was made in a given solvent (enough volume to produce the concentration as shown) and a continuous stream of O<sub>2</sub> passed. A solution of Br<sub>2</sub> (0.04 ml, ~0.73 mmoles) dissolved in the same solvent (2.5 ml) was then added dropwise at r.t. and with continuous stirring.
- b) Dielectric constant ( $\epsilon$ ), J.A. Riddick and W.B. Bunger, in "Techniques of Chemistry" vol. II, A. Weissberger, Ed., 3rd Edition, Wiley-Interscience, N.Y. (1970).
- c) Relative yields are shown. Absolute yields were always >90% based on 1a. All compounds reported gave analytical as well as spectral data fully consistent with the proposed structures. Product distribution were determined in two ways: 1) by quantitative transformation to mixtures of 2b and 3b by reaction with an additional mole of Br<sub>2</sub> followed by integration of the pmr spectrum (100 MHz) of the resulting mixture (the aromatic region consists of two pairs of well separated singlets); and 2) by quantitative catalytic hydrolysis of the mixtures of 2a and 3a to give mixtures of 1- and 2-(3,4-methylendioxyphenyl) propanes followed by integration of the pmr spectrum (100 MHz) of the resulting mixtures in the region above  $\delta$ .
- d) A mixture of bromo-methoxy adducts was also obtained.

As the charge transference complex (c.t.c.) starts to break to give the transition states leading to bromonium ion and phenonium ion a positive charge and a negative charge (bromide ion) start to develop. We believe that the distribution of the positive charge between the olefinic carbon atoms and the bromine depends, for a given substituent, mainly on the polarity of the solvent. Thus a more polar solvent would favor a more highly localized charge which in our case should be at the secondary carbon.<sup>5</sup> Making the reasonable assumption that entrance to the transition state leading to phenonium ion requires a positive charge at the secondary carbon, it is easy to understand that by increasing the polarity of the solvent the rearrangement reaction is favored.

In the case of MeOH, a solvent of much greater polarity than CH<sub>2</sub>ClCH<sub>2</sub>Cl, only ~42% of 3a was obtained suggesting that polarity is not the only contributing factor which determines the product distribution. We believe that in MeOH the positive charge is highly localized on the secondary carbon but since

this solvent is also capable of nucleophilic solvation it competes with the ring for the positive charge. The stronger the solvation the less the proportion of phenonium ion formed.<sup>6</sup> This proposition is in line with recent work by McManus and Peterson who concluded that carbonium ions become more important than cyclic halonium ions as the solvent becomes more capable of nucleophilic solvation.<sup>7</sup>

When the reaction was run in t-buOH only 2a could be detected (>95%). The complete or almost complete selectivity observed in this reaction can only be explained by assuming that the developing positive charge is never or almost never localized at the secondary carbon. This finding also points to the fact that polarity is not the only factor affecting the distribution of the positive charge since in  $\text{CH}_2\text{ClCH}_2\text{Cl}$ , a solvent of comparable dielectric constant, ~68% rearrangement was obtained. Nucleophilic solvation of the developing positively charged species will be, because of steric factors, favored at the primary carbon, precluding therefore the benzene ring to participate.

It had been noted<sup>2</sup> that the product distribution resulting from the reaction of 1a with  $\text{Br}_2$  in  $\text{CHCl}_3$  depended, in part, on the concentration of the reagents. We have found that the importance of this factor varies with the solvent. While in  $\text{CHCl}_3$  a 10-fold dilution produced ~13% increase in 3a, in MeOH the increase was ~60%. No change could be detected in  $\text{CH}_2\text{ClCH}_2\text{Cl}$  even with a 40-fold dilution. Being the reaction of the intermediates with bromide ion a bimolecular reaction, it may be assumed that the rate of this reaction would be reduced upon dilution allowing for some of the bromonium ion to convert into phenonium ion. The increased sensibility of the  $\text{CH}_3\text{OH}$  reaction to dilution when compared to  $\text{CHCl}_3$  could be taken as another indication of the carbonium ion character of the intermediate in solvents of high dielectric constant and nucleophilic solvation capacity.

The observation had also been made that by increasing the concentration of the reagents in  $\text{CHCl}_3$ , the proportion of rearranged products increased.<sup>2</sup> Based upon the fact that the reaction of 1a with  $\text{Br}_2$  in the absence of solvent gives similar results,<sup>3</sup> we may assume that 1a and the products derived from it are, in concentrated solutions, effective co-solvents with  $\text{CHCl}_3$ .

The aforementioned explanation for our results is in contradiction with recent work by Ruasse and Dubois who concluded that "since specific solvation of the cationic part does not exist, the solvent cannot influence significantly the distribution of the positive charge between the olefinic carbon atoms and the bromine."<sup>8</sup> These authors further suggested that it is the substituent character which determines the charge distribution.

In our case however, the substituent is always the same (3,4-methylenedioxybenzyl) and as it has been found in the  $\beta$ -aryl ethyl ester solvolysis, the importance of neighboring phenyl assistance depends not on the solvent but on the ring substituent.<sup>9</sup> If the intrinsic capacity of a given substituent to participate remains the same and the nature of the solvent does not considerably modify the

charge distribution, it would be expected that the product distribution should not be so sensible to solvent effects. If the views of Ruasse and Dubois<sup>8</sup> applied, the only way to explain our results would be by accepting that after the bromonium ion and the phenonium ion are formed in the same proportions in all solvents a rapid equilibrium would be established which would favor one path or the other depending on the solvent. This latter possibility seems much less attractive however. Firstly, if a rapid equilibrium was established after the formation of the intermediates, concentration effects should not be observed; and secondly, accepting that the rate of achieving equilibrium varied from solvent to solvent and knowing that dilution always favors the phenonium ion, why would t-buOH completely revert the equilibrium to favor exclusively or almost exclusively the bromonium ion intermediate?

Work is now in progress to further clarify the role of the solvent in the reactions of 1a with brominating agents.

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#### REFERENCES AND NOTES

1. This is Part II in the series "Chemical Transformations of Abundant Natural Products". For Part I, see M. Garcia, et al., Phytochemistry, in press.
2. Comparable results were recently reported by K. Otsuki and T. Irino, Chem. Pharm. Bull., 23, 646 (1975).
3. A similar reaction of 1a with 1 mole of Br<sub>2</sub> gave a mixture of 2a, 2b, 3a, 3b and ~30% of unreacted 1a. Further, when 1b was treated with Br<sub>2</sub> in CHCl<sub>3</sub>, 2b and 3b were formed in ~88% and ~12% respectively.
4. D. Fain, J. Toullec, and J.E. Dubois, Tetrahedron Letters, 1725 (1974)
5. R.E. Buckles, J.L. Miller, and R.J. Thurmaier, J. Org. Chem., 32, 888 (1967)
6. Reaction of 1a with Br<sub>2</sub> in acetone-water (8:2, v/v) gives ~20% rearrangement only.
7. S.P. McManus and P.E. Peterson, Tetrahedron Letters, 2753 (1975)
8. M.F. Ruasse and J.E. Dubois, J. Am. Chem. Soc., 97, 1977 (1975)
9. F.L. Schadt and P. von R. Schleyer, J. Am. Chem. Soc., 95, 7860 (1973)