SOLVENT EFFECTS IN THE REACTION OF SAFROLE WITH BROMINE.[1]

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While the reaction of safrole (1a) with 1 mol of Br_2 in $CHCl_3$ gave ~65% of 2a along with ~35% of 3a[2], a similar reaction of 1a with 2 moles of Br_2 without solvent gave ~55% of 2b together with ~45% of 3b,[3] 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.
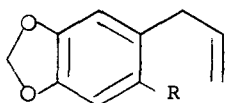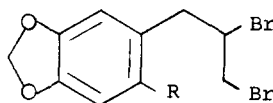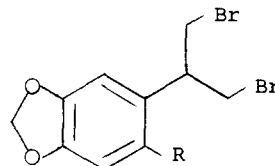
a, R=H; b, R=Br

Based on the work of Dubois et al.,[4] 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:
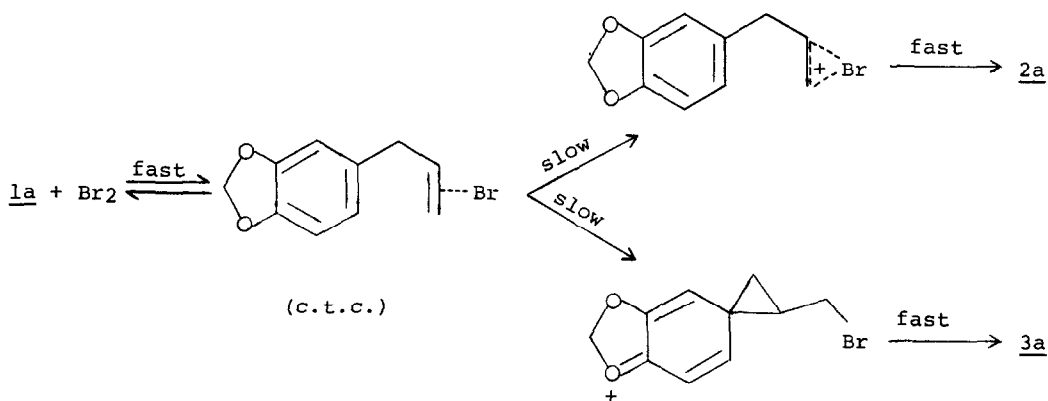
TABLE I. % Product Distribution in the Reaction of <u>1a</u> with Br$_2$.[a]

Solvent(ε)[b]	<u>2a</u>[c]	<u>3a</u>[c]	Initial Concentration of <u>1a</u> (M)x10^2	3a/2a
CCl$_4$ (2.23)	65.8	34.2	22.6	0.52
CHCl$_3$ (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$_2$Cl$_2$ (8.93)	47.0	53.0	22.6	1.12
CH$_2$ClCH$_2$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[d] (32.70)	58.5	41.5	22.6	0.71
	36.4	63.6	2.26	1.75

a) A solution of <u>1a</u> (0.1 ml,~0.68 mmoles) was made in a given solvent (enough
   volume to produce the concentration as shown) and a continuos stream of O$_2$
   passed. A solution of Br$_2$ (0.04 ml, ~0.73 mmoles) dissolved in the same
   solvent (2.5 ml) was then added dropwise at r.t. and with continuos stirring.
b) Dielectric constant (ε), 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 <u>1a</u>.
   All compounds reported gave analytical as well as spectral data fully
   consistent with the proposed structures. Product distribution were deter-
   mined in two ways: 1) by quantitative transformation to mixtures of <u>2b</u> and <u>3b</u>
   by reaction with an additional mole of Br$_2$ followed by integration of the pmr
   spectrum (100 MH$_z$) of the resulting mixture (the aromatic region consists of
   two pairs of well separated singlets); and 2) by quantitative catalytic hydro-
   genolysis of the mixtures of <u>2a</u> and <u>3a</u> to give mixtures of 1- and 2-(3,4-meth-
   ylendioxyphenyl) propanes followed by integration of the pmr spectrum
   (100 MH$_z$) of the resulting mixtures in the region above 3δ.
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.[5] 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 in-
creasing the polarity of the solvent the rearrangement reaction is favored.

In the case of MeOH, a solvent of much greater polarity than CH$_2$ClCH$_2$Cl,
only ~42% of <u>3a</u> was obtained suggesting that polarity is not the only contrib-
uting 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.[6]   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.[7]

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 CH_2ClCH_2Cl, a solvent of comparable dielectric constant, ~68% rearrange-
ment was obtained. Nucleophilic solvation of the developing positively charged
species will be, because of steric factors, favored at the primary carbon, pre-
cluding therefore the benzene ring to participate.

It had been noted[2] that the product distribution resulting from the reaction
of la with Br_2 in $CHCl_3$ depended, in part, on the concentration of the reagents.
We have found that the importance of this factor varies with the solvent. While
in $CHCl_3$ a 10-fold dilution produced ~13% increase in 3a, in MeOH the increase was
~60%. No change could be detected in CH_2ClCH_2Cl 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 CH_3OH reaction to dilution when compared to $CHCl_3$
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 $CHCl_3$, the proportion of rearranged products increased.[2] Based
upon the fact that the reaction of la with Br_2 in the absence of solvent gives
similar results,[3] we may assume that la and the products derived from it are, in
concentrated solutions, effective co-solvents with $CHCl_3$.

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.[8] 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-methylendioxy-
benzyl) and as it has been found in the β-aryl ethyl ester solvolysis, the
importance of neighboring phenyl assistance depends not on the solvent but on the
ring sustituent.[9] 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[8] 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 stablished 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 stablished 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 <u>la</u> with brominating agents.

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., <u>Phytochemistry</u>, in press.
2. Comparable results were recently reported by K. Otsuki and T. Irino, <u>Chem. Pharm. Bull.</u>, <u>23</u>, 646 (1975).
3. A similar reaction of <u>la</u> with 1 mole of Br_2 gave a mixture of <u>2a</u>, <u>2b</u>, <u>3a</u>, <u>3b</u> and ~30% of unreacted <u>la</u>. Further, when <u>lb</u> was treated with Br_2 in $CHCl_3$, <u>2b</u> and <u>3b</u> were formed in ~88% and ~12% respectively.
4. D. Fain, J. Toullec, and J.E Dubois, <u>Tetrahedron Letters</u>, 1725 (1974)
5. R.E. Buckles, J.L. Miller, and R.J. Thurmaier, <u>J. Org. Chem.</u>, <u>32</u>, 888 (1967)
6. Reaction of <u>la</u> with Br_2 in acetone-water (8:2, v/v) gives ~20% rearrangement only.
7. S.P. McManus and P.E Peterson, <u>Tetrahedron Letters</u>, 2753 (1975)
8. M.F. Ruasse and J.E. Dubois, <u>J. Am. Chem. Soc.</u>, <u>97</u>, 1977 (1975)
9. F.L. Schadt and P. von R. Schleyer, <u>J. Am. Chem. Soc.</u>, <u>95</u>, 7860 (1973)