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Products from solvolysis reactions that form (2-phenylcyclopropyl)carbinyl cations

R. Esala P. Chandrasena, David Aebisher and Martin Newcomb*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, IL 60607, USA

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ABSTRACT: Products from solvolytic reactions that form the (2-phenylcyclopropyl)carbinyl cation were determined. The majority of products ($>98\%$) derived from the 1-phenyl-3-butenyl cation, consistent with reports by Wiberg and co-workers. Small amounts of products derived from the 1-phenyl-1-cyclopropylmethyl cation also were found; these products were previously predicted to be formed from reactions of the title cation. Although the 1-phenyl-1-cyclopropylmethyl cation is considerably more stable than the 1-phenyl-3-butenyl cation, it is not kinetically accessible under a variety of solvolytic conditions. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: solvolysis; 2-(phenylcyclopropyl)carbinyl cations

INTRODUCTION

For more than a decade, *trans*-2-phenylmethylcyclopropane (**1**) and related aryl-substituted methylcyclopropanes have been employed in mechanistic studies of hydroxylation reactions catalyzed by cytochrome P450 enzymes (P450s), methane monooxygenase enzymes and related heme-iron and diiron enzymes.[1,2] If radical **2** were formed in an enzyme-catalyzed hydroxylation reaction, then rapid ring opening to radical **3** could occur ($k \approx 3 \times 10^{11}\ s^{-1}$ at ambient temperature),[3] leading ultimately to rearranged alcohol **4** (Scheme 1). Hence the detection of homoallyl alcohol **4** in early enzyme mechanistic studies was taken as evidence for a radical intermediate. In quantitative applications of probe **1** and related cyclopropane substrates in P450 studies, however, the apparent lifetimes of radical intermediates varied by several orders of magnitude, leading to the conclusion that the probe substrates were rearranging at least in part by a cationic pathway.[2] Subsequent studies with probes that differentiated between radical and cationic intermediates demonstrated that cation-derived products indeed were formed in the hydroxylation reactions.[2,4]

After the discovery that cationic intermediates were formed in P450 hydroxylations, our group interpreted the formation of rearranged alcohol **4** in enzyme studies as likely arising in part from a solvolysis-type reaction of the protonated alcohol intermediate **5a** formed by insertion of the elements of OH^+ into a C—H bond in **1**. From the experimental and computational work reported by Wiberg and co-workers,[5,6] cation **5a** was expected to give benzylic cation **6** that led to alcohol **4** (Scheme 2). Others have interpreted evidence for cationic intermediates in enzyme-catalyzed reactions as implicating the formation of free carbocations, possibly by H-atom abstraction to give a radical that is oxidized.[7] In the context of probe **1**, such a sequence would give cation **5b**, but Shaik and co-workers recently predicted that cation **5b** would rearrange to cation **7**, which would lead ultimately to alcohol **8** (Scheme 2).[8,9] If that were the case, then the products from the enzyme reactions might permit a distinction between formation of protonated alcohol **5a** and carbocation **5b** formed by oxidation of a radical. Indeed, Shaik and co-workers concluded that the formation of **4** and absence of **8** demonstrated that carbocations were *not* formed in P450-catalyzed oxidations of probe **1**.[8]

Cation **7** is well known to be a relatively low-energy species, with a stability similar to that of the diphenylmethyl cation.[10] Despite this stability, it is not apparent that a low-energy pathway to **7** exists such that it should be formed from cation **5b**. In fact, Wiberg and co-workers' computations did not predict that cation **7** would be formed,[6] and alcohol products such as **8** have not been reported from previous solvolytic studies that gave **5b**. Nonetheless, early studies of 2-phenylcyclopropylcarbinyl arenesulfonates and trifluoroacetates focused on rates of reactions and not products,[11] and Wiberg and co-workers' product studies were conducted before high-performance gas chromatographic (GC) columns were available.[5] To determine whether alcohol **8** is formed from **5b**, we have conducted a detailed product study of solvolytic reactions that form the (2-phenylcyclopropyl)carbinyl cation. In agreement with Wiberg and co-workers' reports,[5,6] the

**Correspondence to:* M. Newcomb, Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, USA. E-mail: men@uic.edu
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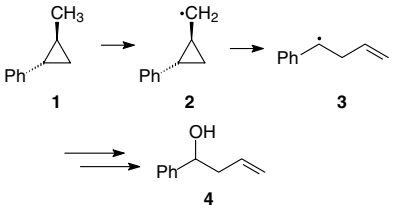
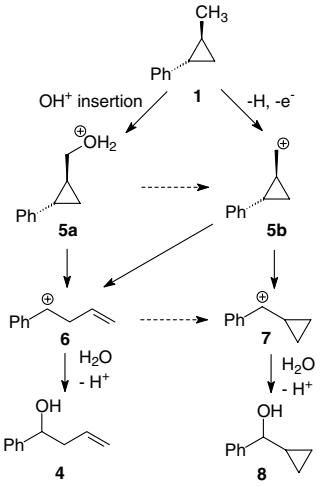


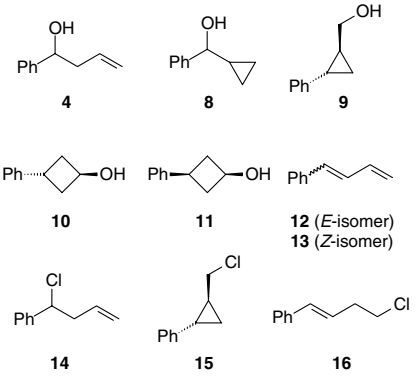
Scheme 1



Scheme 2

reactions gave mainly products derived from benzylic cation **6**. Small amounts of **8** also were produced, but the low yields indicate that this product cannot be expected to form at detectable levels in enzyme-catalyzed reactions that involve cations **5a** or **5b**. Hence the negative result, i.e. the absence of **8** in enzyme reactions, does not permit one to discount the possibility that carbocations were formed in enzyme-catalyzed reactions as Shaik and co-workers proposed.[8,9]

Scheme 3 shows the reactant alcohols and products from solvolysis reactions, all of which are known compounds. For GC and GC–mass spectral characterization, authentic samples of 1-phenyl-3-buten-1-ol[12] (**4**), 1-phenyl-1-cyclopropylmethanol[13] (**8**), (*trans*-2-phenylcyclopropyl)methanol[14] (**9**), *trans*-3-phenylcyclobutanol[6] (**10**) and *cis*-3-phenylcyclobutanol[6] (**11**) were prepared. Reactions of these alcohols with pyridine–acetic anhydride gave acetates for authentication of the products in acetolysis reactions. We also prepared authentic samples of (*E*)-1-phenyl-1,3-butadiene[15] (**12**), 4-chloro-4-phenyl-1-butene[16,17] (**14**), *trans*-2-(phenylcyclopropyl)methyl chloride[16] (**15**) and (*E*)-4-chloro-1-phenyl-1-butene[18] (**16**). (*Z*)-1-Phenyl-1,3-butadiene (**13**) was formed as a minor component (ca 5%) in the preparation of **12**. GC analysis of the alcohols and of the acetates showed that all products were resolved on wide-bore capillary Carbowax 20M columns, with the exception of alcohols **10** and **11** and their respective acetates, which eluted together in a broadened peak (Fig. 1). Diene **12** decomposed slowly on standing and partially decomposed in the GC analysis, and we assume that diene **13** also decomposed partially in the GC analysis.



Scheme 3. Reactant alcohols and products

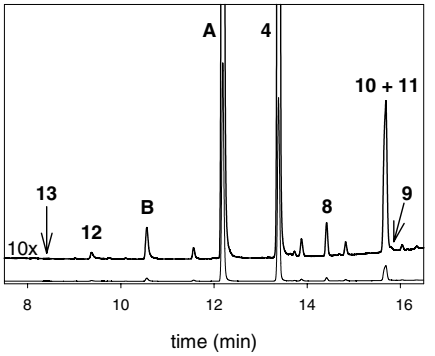


Figure 1. Representative GC trace from a hydrolysis reaction of **11**-OTs. The products from the reaction are labeled. Peak A is the internal standard, 1-phenyl-1-propanol, added after the reaction, and peak B is an impurity in the sample of internal standard

RESULTS AND DISCUSSION

Solvolysis reactions of the tosylates from cyclobutanols **10** and **11**, prepared by the method of Wiberg and co-workers,[5,6] were conducted in water and in acetic acid. The first-formed intermediates of these solvolyses reactions are 2-phenylcyclobutyl cations that rearrange to (2-phenylcyclopropyl)methyl cations.[6] The acetolysis reactions essentially reproduced the studies of Wiberg and co-workers but with an emphasis on products rather than rates.[5,6] Table 1 contains the results. Consistent with the 1969 report,[5] alcohol **4** (in hydrolysis reactions) and acetate **4**-OAc (in acetolysis reactions), from benzylic cation **6**, were by far the major products formed. Alcohol **8** and its acetate also were detected with the aid of high-performance GC. In the hydrolysis reactions, the ratios of **4** to **8** were 80:1 from **10**-OTs and 50:1 from **11**-OTs. In the acetolysis reactions, the ratios of **4**-OAc to **8**-OAc were 360:1 and 220:1 from the respective tosylates. The

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Table 1. Relative % yields of products from solvolysis reactions[a]

Reactant	Conditions	4	8	9	10 + 11	12	13
10-OTs	Hydrolysis[b]	96.3	1.2	0.4	1.2	0.8	0.1
11-OTs	Hydrolysis[b]	86.5	1.7	0.3	10.8	0.6	0.1
10-OTs	Acetolysis[c]	73.0	0.2	0.5	0.6	24.7	1.1
11-OTs	Acetolysis[c]	67.3	0.3	0.2	7.0	23.9	1.3
9-OMs	Hydrolysis[d]	66.4	0.14	2.9	0	26.6	3.3

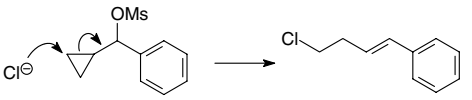
[a] Relative percentage yields are averages of two runs.
[b] Aqueous $NaHCO_3$ solution at reflux for 30 min.
[c] Acetic acid containing NaOAc at 120 °C for 2–3 h; the acetate derivatives of the alcohols were the products obtained.
[d] Solutions of the mesylate were prepared in THF at −20 °C, and the mixtures were added to water at ambient temperature.

very low yields of **8**-OAc are noteworthy because the reactions were conducted at 120 °C. Cation **5b** is a requisite intermediate from the cyclobutyl tosylates,[6] and the solvolytic conditions were much more severe than enzyme-catalyzed reactions.

Reactions of the mesylate of alcohol **9** gave similar results. Mesylate **9**-OMs is unstable, but it and related 2-aryl-substituted-cyclopropylmethanol mesylates can be produced *in situ* at ca −20 °C in THF and reduced with $LiBEt_3H$ to give 2-aryl-1-methylcyclopropanes.[19] Therefore, we prepared THF solutions of **9**-OMs at −20 °C and added the reaction mixtures to water at ambient temperature. The results are given in Table 1. Again, a trace of alcohol **8** could be detected, but the average ratio of alcohol **4** to alcohol **8** was about 500:1. Alcohol **9** was found in 2.9% yield, but it is likely that most of this material resulted from incomplete conversion of **9** to the mesylate. Chloride **14** (0.5%) and traces of chlorides **15** and **16** (ca 0.05% each) were also detected in these reactions.

Dienes **12** and **13** were found in all reactions listed in Table 1, and diene **12** was the second most abundant product in the acetolysis reactions and in the hydrolysis reaction of **9**-OMs. Dienes **12** and **13** apparently are primary products formed by deprotonation of cation **6** in competition with nucleophilic capture. In a control reaction, acetate **4**-OAc gave diene **12** in $< 1\%$ yield when subjected to the acetolysis conditions, demonstrating that **12** and **13** were not secondary products.

A series of reactions with **9**-OMs was conducted that should have been most favorable for formation of cation **7**, which is about 7 kcal mol^{-1} (1 kcal = 4.184 kJ) more stable than cation **6**.[8] Mesylate **9**-OMs was prepared at −20 °C as above, and a small amount of water was added to the reaction mixture, which was then allowed to warm to room temperature. In principle, cations formed in these reactions will react mainly with THF to give oxonium ions that can lose THF to regenerate the cations. The major product formed under these conditions was diene **12**, but small amounts of alcohols **4** and **8** were obtained. For six reactions, the average ratio of **4** to **8** was 86:1, and, when the yields of all products were considered, the average relative yield of alcohol **8** was 0.04%.



Scheme 4

Reactions similar to those described above were conducted with the mesylate **8**-OMs to ensure that alcohol **8** was stable. The only products found were alcohol **8** (98.5% relative yield) and chloride **16** (1.5% relative yield). Importantly, no diene **12** was detected from **8**-OMs; hence diene **12** does not arise from cation **7**.

Traces of chloride products **14**–**16** ($< 1\%$) were detected in the reactions of **9**-OMs and a 1.5% yield of chloride **16** was found in reactions of **8**-OMs. The source of nucleophilic chloride in these reactions was the methanesulfonyl chloride used to prepare the mesylates, and the formation of traces of these chlorides attests to the mild conditions of the reactions and presumed relatively long lifetimes of cationic transients. In the reaction of **8**-OMs, we speculate that chloride **16** arose in part from nucleophilic addition to the cyclopropane ring of the mesylate as shown in Scheme 4.

From the present results, the formation of alcohol **4** from cationic intermediate **5a** produced in an enzyme-catalyzed oxidation of probe **1** clearly is expected. This fact provides sensibility for the results of mechanistic probe studies of oxidizing enzymes. If the only route to homoallylic alcohol products from 2-arylcyclopropylmethane probes was a radical pathway, then the quantitative results from studies with several probes would be confusing. For example, for the P450 2B1 enzyme that has been studied in detail, the variations in the apparent lifetimes of the radical transients would be three orders of magnitude, where some of the radical trapping reactions had effectively zero activation energy.[2]

Unfortunately, the low yields of **8** and **8**-OAc found in this work demonstrate that one cannot reach any meaningful conclusions from the absence of **8** in an enzyme-catalyzed oxidation of probe **1**. The total product yields in the cytochrome P450-catalyzed oxidations of probe **1** are typically in the range of tens to hundreds of nanomoles, and yields of rearranged product **4** are < 10 nmol. From the present results, if all of alcohol **4** arose in a cationic route, one might expect the formation of alcohol **8** in yields < 100 pmol and possibly as low as 1 pmol. These amounts are much smaller than the amounts of numerous components in the product mixture that derive from the enzyme mixtures and buffers.

Hence a negative result from enzyme studies with **1** or related aryl-substituted probes, i.e. a failure to detect **8** and analogues in the products, provides no information about the mechanism of the reactions. Although thermodynamically favored,[10] cation **7** simply is not formed

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appreciably in typical solvolysis reactions that produce the (2-phenylcyclopropyl)carbinyl cation. Moreover, the formation of alcohol **4** from cation **6** confirmed in the present work demonstrates that detection of **4** from enzyme-catalyzed oxidations of **1** does not provide conclusive evidence for a radical intermediate. Simple aryl-substituted methylcyclopropanes might be good radical clocks when one knows the mechanism, but they are poor mechanistic probes if one does not. More complex probes that clearly differentiate between radicals and cations are better mechanistic tools.[4]

EXPERIMENT

Solvolysis reactions of 10-OTs and 11-OTs. Solutions of *trans*- or *cis*-3-phenylcyclobutanol tosylates[5] (0.01 g, 0.037 mmol) in water (4 ml) with $NaHCO_3$ (0.1 g) were heated at reflux for 30 min. The cooled solutions were extracted with diethyl ether (3×25 ml) and the ether phase was washed with brine and dried over $MgSO_4$. Products were identified by GC and GC–mass spectral comparisons with authentic compounds. GC response factors were obtained with authentic compounds, and yields in micromoles for each product were determined against the internal standard 1-phenyl-1-propanol added after the extractive work-up. Acetolysis reactions were conducted in a similar manner in solutions of acetic acid (4 ml) containing 0.1 g of NaOAc, which were heated at 120 °C for 2–3 h. Yields in Table 1 are averages for two determinations.

Hydrolysis reactions of 9-OMs. Alcohol **9** (0.053 g, 0.36 mmol) was converted to its mesylate by reaction with MsOCl (35 µl, 0.36 mmol) in THF (5 ml) containing Et_3N (123 µl, 0.88 mmol) at −20 °C. After 1 h, the reaction mixtures were poured into water (60 ml) at room temperature. The reaction mixture was worked up and analyzed as described above.

Acknowledgment

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