Tetrahedron Vol. 41, No. 19, pp. 3973 to 3978, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

FREE RADICAL CYCLIZATION IN MOLECULAR AGGREGATES

DENNIS G. WUJEK AND NED A. PORTER*

Paul M. Gross Chemical Laboratory

Duke University

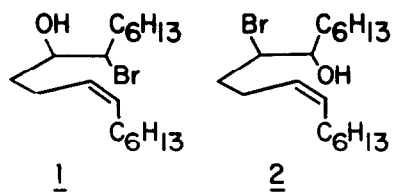
Durham, North Carolina 27706

(*Received in Germany* 6 *February* 1985)

Abstract: The cyclization of free radicals has been investigated in micelles and multilamellar lipid bilayer vesicles. The substrate for cyclization is the amphipathic bromohydrin 7-bromo-octadec-11-ene-8-ol, **1**. The radical is generated from **1** in aqueous micelles or vesicles by $NaBH_4/Bu_3SnCl$. Four diastereomeric cyclopentanol products are formed in the 5-exo cyclization and the distribution of these products depends on the solvent and aggregate. Product distributions for cyclization in all media which have an aqueous/organic interface are significantly different from product distributions obtained for reactions in homogeneous media.

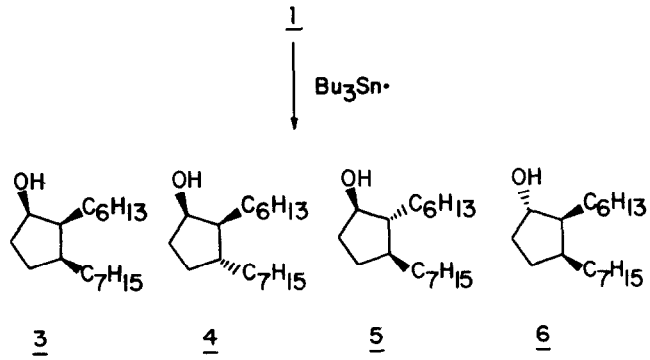
We recently reported an example of the influence of molecular aggregates on the diastereoselectivity of radical pair coupling(1). In this study we observed that aggregates such as micelles and lipid bilayer vesicles influenced the stereochemical course for the decomposition of an amphipathic diazene incorporated within these aggregates. We report here a study of the effect of molecular aggregates on free radical cyclization. Our results support the notion that an aqueous-organic interface can induce stereoselectivity in the formation of diastereomeric cyclization products.

Bromohydrin regioisomers **1** and **2** were prepared by standard procedures from 1,5-hexadiyne(2) and readily separated by normal phase high-pressure liquid chromatography.



1 **2**

Radical cyclizations were carried out under argon in various solvent conditions (Table I) utilizing the catalytic $NaBH_4/Bu_3SnCl$ system(3) to generate Bu_3SnH *in situ*. Bromohydrin **1** was typically 1.40 mM in the benzene and pH 10 buffer experiments and 5 mole % based on the amphipathic host in the runs in molecular aggregates. The resultant diastereomeric cyclopentanol product mixture **3-6** was analyzed by normal phase HPLC or by gas chromatography.



3 4 5 6

Table I. Product Distributions for Tributyltin Hydride Reduction of 1

Temperature	Solvent Conditions[a,b]	Mole Fraction Cyclopentanols 3-6			
		3	4	5	6
60	Benzene[c]	0.20	0.11	0.39	0.30
60	pH 10 Buffer	0.16	0.11	0.36	0.37
30	0.03 M DPPC[d]	0.10	0.12	0.23	0.55
60	0.03 M DPPC[d]	0.10	0.12	0.23	0.55
30	20% mol% cholesterol in 0.03 M DPPC	0.12	0.11	0.24	0.53
60	0.08M SDS[e]	0.10	0.11	0.24	0.55

[a]All DPPC and SDS experiments in pH 10 buffer.

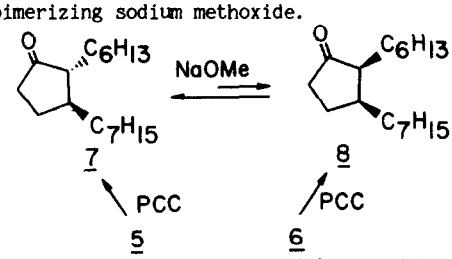
[b]Typically, 1.5 eq Bu_3SnCl and 100-150 eq. $NaBH_4$ based on bromohydrin. Workup after 12-24 hr reaction time.

[c]1.5 eq Bu_3SnH with 0.5 eq AIBN initiator.

[d]Multilamellar vesicles of dipalmitoylphosphatidylcholine

[e]Sodium dodecylsulfate micelles

Product stereochemistries were assigned by ^{13}C NMR(4). Additionally, cyclopentanols 5 and 6 were individually oxidized to the corresponding cyclopentanones 7 and 8 which were known to exist in a 90/10 equilibrium mixture in the presence of epimerizing sodium methoxide.



Comparison of HPLC retention times for the equilibrium mixture with the individual cyclopentanones supported the spectral stereochemical assignments of the alkyl substituents for the cyclized products.

Based on previous studies of stereocontrol in free radical cyclization reactions(5), one might expect to obtain cyclopentanol 6 as the predominant product in the cyclization of 1 in an isotropic medium. In benzene, at 60°C, cyclopentanol 5 is seen to be formed with slight preference over 6 with smaller

amounts of products **3** and **4** being formed. A differential effect is observed, however, at 60° in the cyclization of **1** which has been incorporated into SDS micelles or DPPC multilamellar vesicles(6,7). In these instances, the most amphipathic cyclopentanol, **6**, is clearly seen to be the preferred major product.

These observations may be reasonably explained considering the amphipathic character of a lipid aggregate. In the organized lipid aggregate, one would expect the most amphipathic transition state, **9**, to be favored (Figure 1). Here, the hydroxyl is directed towards the aqueous phase and the lipophilic alkyl groups are directed towards the hydrophobic region. Conversely, **10** is an example of a disfavored, higher energy transition state where the non-polar alkyl group is forced into the polar aqueous phase. This argument may apply in a similar manner for transition states leading to minor products **3** and **4**. It follows then that one might tailor a substrate to meet the desired stereochemical result by the judicious choice of polar and non-polar substituents (R_1, R_2, R_3 in Figure 1) which can serve to anchor the requisite transition state within the aggregate.

Attempts were made to enhance the aggregate-induced diastereoselectivity observed in the cyclization of **1**. However, increasing the rigidity of the bilayer medium with the addition of 20 mol% cholesterol(8) and/or lowering the reaction temperature to 30° had virtually no effect on the product distribution.(9) These results suggest that the dominant effects which determine product selectivity in the cyclization are at the water/lipid interface of the aggregate system and not in the lipophilic region of the medium. This is consistent with the fact that virtually the same product distribution is observed in a DPPC lipid bilayer as is seen when the cyclization is carried out in the less ordered SDS micellar environment.

Interestingly, we note that the molar fraction of cyclopentanol **4** remained virtually constant throughout all the experiments. As a result, in going from benzene to DPPC or SDS micelles, the more amphipathic cyclopentanol **6** is formed only at the expense of products **3** and **5**. This might point to a possible 1,3 interaction which may be inherently important in affecting diastereocontrol within this particular system.

We have shown here that lipid aggregates may be utilized to exert stereocontrol in a reaction which yields diastereomeric products. It is suggested that stereocontrol of this sort may play an important role in the biosynthesis of some natural products since many enzymatic systems are membrane bound(10). The results reported here offer hope that lipid aggregates may eventually be useful in controlling stereochemistry for synthetic applications(11). One may envision designing substrates compatible with the oriented amphipathic environment to induce the desired regio- and stereoselectivity in organic reactions(12). Interests along these lines are currently being pursued in our laboratories.

EXPERIMENTAL

Preparation of Bromohydrin substrate

7,11-Octadecadiyne. In a 1-l round-bottomed flask equipped with mechanical stirrer, addition funnel, and KOH drying tube was prepared a solution of sodium amide from 10.0 g of sodium dissolved in 500 mL liquid ammonia at -78° with catalytic ferric nitrate. To the vigorously stirred solution was added in dropwise fashion over 20 min 4.00 g (0.051 moles) 1,5-hexadiyne dissolved in 30

mL dry DMSO. An additional 150 mL DMSO was then added over a period of 30 min. At this point, hexyl bromide addition was begun with the reaction flask being partially submerged in the dry ice/acetone cooling bath. Hexyl bromide (67.0 g, 0.406 moles) was carefully added over 30 min. The mixture was left to stir and gradually warm overnight. Workup then followed the same procedure as that used in the preparation of 1,5-hexadiyne.(2) Vacuum distillation afforded 5.42 g (43%) 7,11-octadecadiyne, bp 111-115°, 0.35 mmHg (known, bp 167-168°, 7 mm Hg).

7,11-Octadecadiene. Hydrogenation of the requisite diyne was carried out with Lindlar's catalyst in dry methanol. Typically, the reaction was run on 500 mg scale in 20 mL methanol using ca. 50 mg catalyst followed by workup after 36 hr. Conversion to the desired diene was virtually quantitative. Reactions on a larger scale proved to be sluggish and led to complex product mixtures.

7,8-epoxyoctadec-11-ene. To a magnetically stirred solution of 1.0 g (4.00 mmoles) of 7,11-octadecadiene dissolved in 25 mL chloroform at 0° under argon was added an equivalent amount of m-chloroperoxybenzoic acid (690 mg) dissolved in 5 mL chloroform via syringe over a 15 min period. After 3 hr, an additional 0.5 eq mcpba was added to further conversion. The reaction was allowed to warm to room temperature and worked up in the usual way. The desired monoepoxide was isolated in 56% yield based on reacted starting diene following purification on a Waters 1-in Prep column (hexane/ethyl acetate, 97/3).

Preparation of Bromohydrins 1 and 2.

The method employed was a modification of a procedure used by Alt and Barton.(13) To a solution of 600 mg (2.25 mmoles) of 7,8-epoxyoctadec-11-ene dissolved in 25 mL chloroform was added 15 mL of 48% aqueous HBr. The mixture was vortexed for 15 min at room temperature and worked up as described previously. Purification on a Waters 1-in Prep column (hexane/ethyl acetate, 95/5) afforded a 92% yield of the regioisomeric mixture **1/2** as a clear oil. The bromohydrins were HPLC-separated on a Whatman Partisil 10-μ Magnum column (hexane/ethyl acetate, 97/3) with **1** eluting first. A minor amount of erythro product was seen to elute intermediate to isomers **1** and **2**. Both bromohydrins were individually reacted with Bu_3SnH. Only **1** was seen to yield cyclized product thus establishing bromohydrin regiochemistry. ^1H NMR decoupling experiments supported the assigned structures. Anal Calcd for $C_{18}H_{35}OBr$: C, 62.24; H, 10.16. Found: **1**: C, 62.20; H, 10.09; **2**: C, 62.20; H, 10.00.

Bromohydrin Cyclizations.

In benzene. A two-necked 25 mL round-bottomed flask equipped with magnetic stirrer and argon inlet/outlet was charged with 5.0 mg (0.014 mmoles) **1** dissolved in 10 mL dry benzene. The mixture was deoxygenated by bubbling argon through an airstone directly into the solution for 10 min at the reaction temperature. The airstone was removed from the solution, a catalytic amount of AIBN added (ca. 2 mg) and the system maintained under positive argon pressure. At this point, 6.4 mg (0.022 mmoles) Bu_3SnH were added to the mixture via syringe and progress of the reaction monitored by TLC (hexane/ethyl acetate, 90/10). After 24 hr, the reaction was worked up following the Jacobus(14) procedure and the product mixture analyzed by GC and HPLC.

In DPPC liposomes. A solution of 5.0 mg (0.014 mmoles) of **1**, 240 mg (0.327 mmoles) DPPC, and 7.0 mg (0.022 mmoles) Bu_3SnCl in 20 mL pH 10 buffer was vortexed above 40°C until a homogeneous mixture of multilamellar vesicles resulted. This generally required gentle warming with a heat gun and vortexing for about 5 min. The solution was then deoxygenated as described above. Subsequently, 50 eq (based on **1**) of $NaBH_4$ freshly dissolved in a minimal amount of pH 10 buffer were added to the reaction vessel via syringe. An additional 25 eq $NaBH_4$ were added every 6-8 hr to ensure completion. All starting material was consumed in both the 30° and 60° runs within 24 hr with the latter conversion being more facile. Workup consisted of a Folch extraction(15) followed by a flash silica column (hexane/ethyl acetate, 50/50) to prepare the sample for product analysis.

In pH 10 buffer. To a deoxygenated solution of 5.0 mg (0.014 mmoles) **1** and 7.0 mg (0.022 mmoles) Bu_3SnCl in 10 mL pH 10 buffer was added 50 eq $NaBH_4$ freshly dissolved in a minimal amount of pH 10 buffer. Every 6-8 hr, an additional 25 eq were added. After 12 hr, the reaction mixture was extracted with ether (4 x 10 mL) and the combined organic extracts worked up following the Jacobus procedure.

In SDS micelles. To a solution of 5.0 mg (0.014 mmoles) **1** dissolved in 4.5 mL pH 10 buffer was added 104 mg (0.361 mmoles) SDS and 7.0 mg (0.022 mmoles) Bu_3SnCl. The mixture was vortexed with gentle warming to afford a clear solution which was prone to frothing. The mixture was deoxygenated in the usual way and 50 eq $NaBH_4$ dissolved in pH 10 buffer were added. An additional 25 eq of $NaBH_4$ were added at the 4 hr and 8 hr time points with the solution turning a pale yellow over the course of the reaction. After 10 hr, the reaction mixture was diluted with 450 mL water and extracted with 700 mL ether (add NaCl to break up emulsion). The organic extract was dried over $MgSO_4$, solvent removed in vacuo, and the mixture analyzed for product composition.

Cyclopentanol Characterization

Relative substituent stereochemistry about the cyclopentane ring was established by ^{13}C NMR (60 MHz, $CDCl_3$). Experimentally observed chemical shifts for the quaternary carbons of the cyclized products compared favorably with values calculated for 2,3-disubstituted cyclopentanols where substituents at C-2 and C-3 on the ring were assumed to be long-chain alkyl groups.(4,16)

Cyclopentanol	Observed and (Calcd value)		
	C-1	C-2	C-3
3	75.5(73.9)	48.2(46.7)	40.0(40.1)
4	74.7(75.7)	51.7(51.8)	42.1(44.1)
5	79.5(80.3)	55.0(54.4)	44.8(45.2)
6	78.0(78.5)	51.3(49.3)	40.2(39.0)

3: Anal Calcd for $C_{18}H_{36}O$: C, 80.53; H, 13.52. Found: C, 80.81; H, 13.44.

Pyridinium chlorochromate oxidation of each cyclopentanol to the corresponding cyclopentanone and subsequent treatment with 20 mol % (based on cyclopentanone) sodium methoxide in methanol afforded an equilibrium mixture of cyclopentanones **7** and **8** which were separated by HPLC: Altex Ultrasphere 5μ silica column; hexane/ethyl acetate, 98/2. Cyclopentanone **7** was seen to elute first.

Product Analysis

In all cases, both HPLC and GC analyses of the product mixtures were made. The cyclopentanols were separated by HPLC on an Altex Ultrasphere 5μ silica column with hexane/ethyl acetate, 99/1, and eluted in the following order: **3**, **4**, **5**, **6**. GC analyses were carried out on a Hewlett-Packard 5790A Series instrument using a Carbowax 20M column (elution order: **4**, **5**, **3**, **6**). Cyclizations of **1** carried out in the presence of eicosanol as an internal standard in benzene and DPPC runs indicated that the product mixtures were generally isolated in 75-80% yield including uncyclized reduced material which was found to account for 15-20% of the total product mixture.

References and Notes

1. W. J. Brittain, N. A. Porter and P. J. Krebs. J. Am. Chem. Soc., **106**, 7652 (1984).
2. L. Brandsma, Preparative Acetylenic Chemistry, p. 114, Elsevier Publishing Co., Amsterdam, (1971).
3. E. J. Corey, J. W. Suggs. J. Org. Chem., **40**, 2554 (1975).
4. M. Christl, H. J. Reich, J. D. Roberts. J. Am. Chem. Soc., **93**, 3463 (1971).
5. A. L. J. Beckwith. Tetrahedron, **37**, 3073 (1981).
6. M. K. Jain, R. C. Wagner. Introduction to Biological Membranes, John Wiley & Sons, New York (1980).
7. C. Tanford. The Hydrophobic Effect, 2nd ed., John Wiley & Sons, New York (1980).
8. See reference 6, page 101.
9. The gel-to-liquid crystalline phase transition temperature (T_c) for DPPC is 41°C.
10. J. H. Fendler. Membrane Mimetic Chemistry, John Wiley & Sons, Inc., (1982).
11. Significant control of stereochemistry in radical cyclization would be useful in the construction of the prostaglandins. See, for example, E. J. Corey, C. Shih, and K. Shimoji. Tet. Lett., 5013 (1984).
12. Recent attempts to control reactivity in non-radical cyclizations in micelles have been reported. B. C. Clark, T. S. Chamblee, G. A. Iocabucci. J. Org. Chem., **49**, 4557 (1984).
13. G. H. Alt, D. H. R. Barton. J. Chem. Soc., 4284 (1954).
14. J. E. Leibner, J. Jacobus. J. Org. Chem., **44**, 449 (1979).
15. J. Folch, M. Lees, and G. H. Sloane-Stanley, J. Biol. Chem., **226**, 497 (1957).
16. L. P. Lindeman, J. Q. Adams. Anal. Chem., **43**, 1245 (1971).

Fig. 1
Possible Transition States