was provided by the Office of Basic Energy Sciences, Division of Chemical Sciences, US Department of Energy.

Supplementary Material Available: Experimental details and a table of ketonic decarboxylations with lead dioxide catalysts (2 pages). Ordering information is given on any current masthead page.

Diastereoselectivity in Radical Pair Recombination in Lipid Bilayers

W. J. Brittain, N. A. Porter,* and P. J. Krebs

Department of Chemistry, Duke University
Durham, North Carolina 27706
Received September 6, 1984

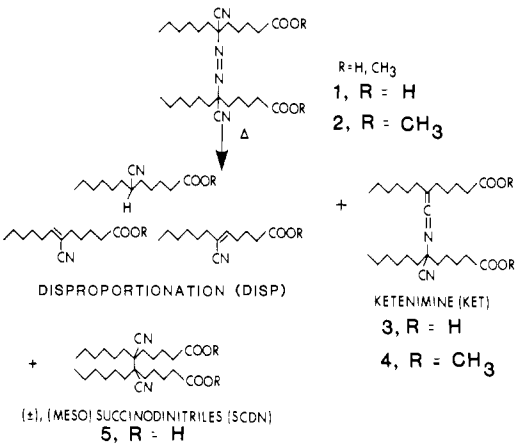
The reactions of free radicals or radical pairs in solution frequently occurs with loss of stereochemistry. Thus, while many radical reactions proceed in high yield, the lack of stereochemical control inherent in these processes has made radical routes unattractive for use in many conversions.[1] One potential solution to the control of stereochemistry in free radical processes is to utilize intermolecular forces to orient radicals or radical pairs. Thus one might anticipate that molecular aggregates such as micelles or the lipid bilayer could exert a stereochemical influence on the course of free radical processes. In this communication, we report on the stereochemical course of diazene decomposition in multilamellar lipid vesicles (MLV) prepared from dipalmitoylphosphatidylchloline (DPPC). We have chosen radical pairs from diazenes as our initial probe of stereochemistry since the behavior of these species is well understood in solution[2] and in the crystal[3] and we have chosen MLVs from DPPC since these molecular aggregates have been thoroughly studied.[4]

The major products of thermal or photochemical decomposition of **1** in DPPC vesicles in water or its methyl ester **2** in chlorobenzene are shown in Scheme I. The ketenimine product **3** is unstable in water and gives a mixture of hydrolysis products although the corresponding methyl ester **4** can be completely characterized. A mild lithium hydroxide hydrolysis of **4** provides the free acid **3** along with substantial amounts of ketenimine hydrolysis products.

The two diastereomers (meso and *dl*) of the succinodinitrile (SCDN) coupling product(s) **5** can be readily separated by HPLC. Stereochemical assignment of the diastereomers of **5** was made by photolysis[3,5] of the known (±)-**2** in a methylcyclohexane/diethyl ether glass at −196 °C. Only one product diastereomer was observed after 5.5 h of photolysis and this product was assigned the (±) stereochemistry.[3]

Diazene decomposition in DPPC vesicles were carried out under degassed conditions and were run to complete diazene decomposition.[6] Product analyisis was performed by reverse-phase HPLC on a C-18 column with solvent methanol/water/acetic acid (750/250/2). Mass balance for decompositions in aqueous emulsions (DPPC vesicles) was low (~50%) and the hydrolytic instability of product ketenimine in the aqueous media is the major cause of this low product balance. Aliquots taken during the thermolysis of **1** in DPPC emulsions indicate that the amount of

Scheme I



ketenimine reaches a maximum during the first half-life of diazene decomposition and then steadily decreases to zero while, in contrast, the disproportionation and coupling products steadily increase over time.[7]

Diastereoselectivity of radical pair coupling in lipid vesicles was studied over the temperature range 29–80 °C. The results for diazene decomposition are summarized in Table I. Diastereoselectivity is expressed as the product ratio (±)-**5**/*meso*-**5** and as diastereomeric excess, % de, in Table I. The results suggest that the mode of decomposition (60 °C thermolysis or 59 °C photolysis) does not influence product stereochemistry and we thus conclude that diazene photoisomerization does not play an important role in determining the stereochemical outcome of the reaction. One striking feature of the results presented in Table I and Figure 1 is the magnitude of stereochemical preservation in the coupling products and the differential degree of diastereoselectivity observed from (±)-**1** as compared to *meso*-**1**. Thus, the diastereomeric excess for decomposition of the (±)-diazene is as high as 72% and the meso diastereomer gives a maximum diastereomeric excess of 50%. These results in lipid bilayer are to be compared with decomposition of the diazene methyl esters **2** (2 mM) in chlorobenzene at 60 °C. Under these conditions, (±)-**2** gives a SCDN coupling product ratio of (±)/meso = 1.16 ± 0.02 (% de = 7.4) while meso **2** gives (±)/meso = 0.95 ± 0.1 (% de = 2.6). These results are typical of radical pair reactions in solution and illustrate the low stereochemical preservation generally observed in isotropic fluid.[2]

It should also be noted that significantly enhanced diastereoselectivity is observed for decomposition of **1** alone in pH 7 buffer. Thus (±)-**1** (1 mM in pH 7 phosphate buffer with 0.1 mM EDTA) at 60 °C gives a (±)/meso SCDN ratio of 2.13 ± 0.1 (36% de) while *meso*-**1** yields SCDN in a (±)/meso ratio of 0.52 ± 0.1 (32% de).[8] While this enhanced diastereoselectivity in aqueous buffer is itself surprising, there are aspects unique to diazene chemistry in DPPC bilayers that deserve emphasis. Namely, the bilayer exerts a differential influence on the diazene diastereomers which manifests itself in the kinetics (see ref 5) and the radical coupling.

The high diastereoselectivity of radical pair coupling observed in lipid bilayers has no counterpart in fluid media. It seems likely, based on analogous work carried out in crystals and glasses,[3] that the enhanced stereoselectivity has its roots in the reduced mobility of the radicals in this medium of high microviscosity.[9,10] In this

(1) An exception to this general statement are free-radical cyclizations that lead to a predictable stereochemical outcome. See: Beckwith, A. L. J.; Ingold, K. U. In "Rearrangements in Ground and Excited States"; deMayo, P., Ed.; Academic Press: New York, 1980.

(2) Greene, F. D.; Berwick, M. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 867–874.

(3) (a) Bartlett, P. D.; McBride, J. M. *Pure Appl. Chem.* **1967**, *15*, 89–107. (b) Jaffe, A. B.; Skinner, K. J.; McBride, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 8510.

(4) Fendler, J. H. "Membrane Mimetic Chemistry"; Wiley: New York, 1982.

(5) The stereochemistry of the diazenes was established by resolution of the (±)-diazene quinine salt. See: Petter, R. C.; Mitchell, J. C.; Brittain, W. J.; McIntosh, T. J.; Porter, N. A. *J. Am. Chem. Soc.* **1983**, *105*, 5700.

(6) 10% diazene in 10 mg of DPPC was vortexted in 1 mL of phosphate buffer to form vesicles. Photolysis was with a 900-W xenon source.

(7) We have purified ketenimine **3**, formed by hydrolysis of **4**, and have carried out thermal decomposition of this unstable compound in DPPC liposomes at 60 °C. Small amounts (<10%) of the SCDN products result from this decomposition but the primary products formed appear to be ketenimine hydrolysis products. We thus believe that this secondary decomposition does not contribute significantly to the product stereochemistry.

(8) A complete study of diazene decomposition in water (pH 7 and 10) will be published at a later date.

(9) We thank Professor J. M. McBride for helpful discussions.

(10) Tanford, C. "The Hydrophobic Effect, Formation of Micelles and Biological Membranes", 2nd ed.; Wiley-Interscience: New York, 1980; pp 42–49, 133, 136.

0002-7863/84/1506-7652$01.50/0

Table I. Diastereoselectivity of Radical Recombination

	meso-1		(±)-1	
	(±)/meso[b]	% de[c]	(±)/meso[b]	% de[c]
29 °C, hν	0.43 ± 0.1 [3]	40 (meso)	6.23 ± 0.65 [2]	72 (±)
39 °C, hν	0.33 ± 0.07 [1]	50 (meso)	6.05 ± 0.15 [1]	71 (±)
49 °C, hν	0.51 ± 0.06 [1]	32 (meso)		
59 °C, hν	0.59 ± 0.06 [2]	26 (meso)	6.00 ± 0.86 [3]	71 (±)
60 °C	0.78 ± 0.05 [2]	12 (meso)	5.24 ± 0.25 [2]	68 (±)
70 °C	1.09 ± 0.11 [4]	4 (±)	3.74 ± 0.47 [4]	58 (±)
80 °C	1.04 ± 0.11 [3]	2 (±)	1.84 ± 0.46 [2]	30 (±)

[a] All data from decomposition of diazene 1 in DPPC. [b] Mean ± standard error; the number of separate experiments on which the mean was based given in brackets. [c] De = diastereomeric excess with the predominant diastereomer indicated in parentheses.

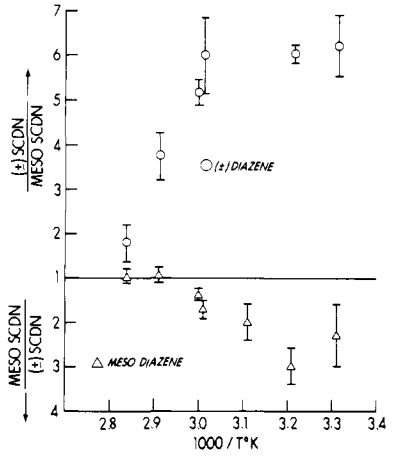


Figure 1. Product ratio for decomposition of (±)- and meso-1 in DPPC multilamellar vesicles. Decomposition is by thermolysis above 59 °C and by photolysis at 59 °C and below.

regard, one might anticipate that diastereoselectivity would be a function of the nature of the molecular aggregate and the position of the reactive pair in the aggregate.

Reversible Three-Electron Redox Couple Based on Os(VI)/Os(III)

David W. Pipes and Thomas J. Meyer*

The University of North Carolina
Department of Chemistry
Chapel Hill, North Carolina 27514

Received August 3, 1984

Recent work on polypyridyl–aquo complexes of Ru and Os has shown that stepwise oxidation can occur through a series of oxidation states with the retention of a common coordination number.[1] One of the surprising features about these redox couples is that an extended series of oxidation states can appear over a relatively narrow potential range because of stabilization of the higher oxidation states by proton loss and metal–oxo formation. For example, the couples interrelating Os(II) to Os(VI), through Os(III), Os(IV), and Os(V) in the sequence $(bpy)_2Os^{II}(H_2O)_2^{2+}$ to $(bpy)_2Os^{VI}(O)_2^{2+}$ (bpy is 2,2′-bipyridine) occur over the potential range of 0.16 to 0.78 V vs. SSCE at pH 2.0 (saturated sodium chloride calomel electrode).[1b] We report here what must represent an extreme case of such behavior; polypyridyl–aquo complexes of Os in which oxidation states VI to III are interrelated by a *three*-electron process with *all* three electrons being gained at the same potential.

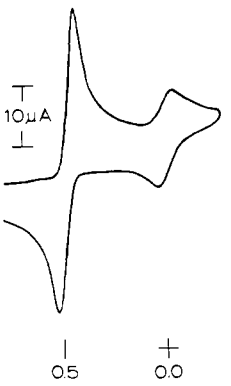


Figure 1. Cyclic voltammogram of 1×10^{-4} M solution of $(trpy)Os^{VI}(O)_2(OH)^+$ in 0.1 M $HClO_4$ (pH 1) at an oxidatively activated Tokai glassy carbon electrode vs. SSCE at 100 mV/s.

The complex $[(trpy)Os^{VI}(O)_2(OH)]^+$ was prepared by a route similar to that already described for $(phen)Os^{VI}(O)_2(OH)_2$ (phen is 1,10-phenanthroline).[2] The product was purified by dissolution and reprecipitation with ClO_4^- from H_2O to give a light tan powder. Characterization of the product included elemental analysis,[3] ^1H NMR, and infrared spectroscopy. The ^1H NMR was consistent with a diamagnetic, Os(VI) (d^2) system with terpyridine resonances as a doublet at 9.5 ppm, integrating to two protons, a multiplet at 8.7 ppm, integrating to five protons, and a pair of triplets, integrating to two protons each at 8.6 and 8.1 ppm. In the infrared spectrum, the appearance of a single band at 840 cm^{-1} is consistent with the appearance of the asymmetric stretch of the trans $O{=}Os^{VI}{=}O$ group.[2]

As shown in Figure 1, cyclic voltammetric studies on the Os(VI) salt in water using an oxidatively activated glassy carbon electrode[4] provide evidence for redox processes at $E_{1/2}$ = 0.44 and −0.01 V vs. SSCE, pH 1.0. From the relative peak heights, the wave appearing at the more positive potential appears to be multielectron in nature. Coulometric studies in 0.1 M $HClO_4$ using a graphite cloth working electrode show that the first reduction wave corresponds to a n = 3 (±0.1) reduction and the second to a n = 1 (±0.08) reduction. Further evidence of a three-electron reduction has been obtained from rotated-disc electrode measurements at a glassy carbon electrode, where the limiting current ratio for the two reduction waves is 3:1. Cyclic voltammetric scan-rate studies of the multielectron wave show that, as the scan rate is decreased from 100 to 10 mV/s, the difference in peak potentials, $\Delta E_p = E_{p,a} - E_{p,c}$, falls from 55 to 26 mV, nearly the theoretical value, ΔE_p = 20 mV, expected for a three-electron wave. Similar studies on the complex $(phen)Os^{VI}(O)_2(OH)_2$ also show the presence of a three-electron redox couple at $E_{1/2}$ = 0.39 V followed by a one-electron reduction at −0.30 V vs. SSCE at pH 1.0, but the three-electron step is less well-defined electrochemically.

The electrochemical observations point to the remarkable fact that, in these coordination environments, Os(VI) is reduced directly

(1) (a) Takeuchi, K. J.; Thompson, M. S.; Pipes, D. W.; Meyer, T. J. *Inorg. Chem.* **1984**, *23*, 1845. (b) Takeuchi, K. J.; Samuels, G. J.; Gersten, S. W.; Gilbert, J. A.; Meyer, T. J. *Inorg. Chem.* **1983**, *22*, 1409. (c) Moyer, B. A.; Meyer, T. J. *Inorg. Chem.* **1981**, *20*, 436.

(2) (a) Galas, A. M. R.; Hursthouse, M. B.; Beheman, E. J.; Midden, W. R.; Green, G.; Griffith, W. P. *Transition Met. Chem. (Weinheim, Ger.)* **1981**, *6*, 194. (b) Chang, C. H.; Midden, W. R.; Deety, J. S.; Beheman, E. J. *Inorg. Chem.* **1979**, *18*, 1364.

(3) Elemental analysis of $[(C_{15}H_{11}N_3)Os(O)_2(OH)](ClO_4)$. Found: C, 31.29; H, 2.12; N, 7.19. Calcd: C, 31.50; H, 2.12; N, 7.35.

(4) Cabaniss, G. E.; Diamantis, A. A.; Murphy, W. R., Jr.; Linton, R. W.; Meyer, T. J. *J. Am. Chem. Soc.*, in press. Activation of the Tokai glassy carbon electrode was accomplished by holding the cell potential at +1.6 V vs. SSCE in 0.1 M $HClO_4$ for 5 min, followed by two cyclic scans to −0.2 V. This procedure was repeated twice to achieve maximum activation. At a polished, unactivated electrode the waves were much broader and peak to peak separations much larger, 188 mV compared to 55 mV at a sweep rate of 100 mV/s. The surface area of the polished electrode, determined by rotated-disc experiments, was 0.0712 cm^2.

0002-7863/84/1506-7653$01.50/0