indicates that the complex is diamagnetic and that both porphyrin rings are equivalent; however, the resonance for the bound diazene protons could not be unambiguously assigned. Because the protons of diazene complexes are normally shifted substantially downfield,[21] this shift may counteract the porphyrin ring current effect, causing the peak to occur in the range of and be obscured by porphyrinic signals. In support of this formulation, oxidation of the diazene complex, $Ru_2(N_2H_2)$, by an additional equivalent of *tert*-butyl hydroperoxide (under argon) yields the stable dinitrogen complex, $Ru_2(N_2)$.

Oxidation of $Ru_2(NH_3)_2$ with slightly more than 1 equiv of *tert*-butyl hydroperoxide yields a mixture of $Ru_2(N_2H_4)$, $Ru_2(N_2H_2)$, and $Ru_2(N_2)$, as well as unreacted $Ru_2(NH_3)_2$. Thus the four complexes are interconvertible via successive two-electron oxidations. We are exploring chemical and electrochemical means for their interconversion, as well as studying the detailed steps involved in these oxidations. In addition, attempts to interconvert the complexes via reductions, and attempts at electrocatalytic dinitrogen reduction using cofacial diporphyrins are currently in progress.

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(20) ^{1}H NMR ($Ru_2(N_2H_2)$, C_6D_6, ppm): porphyrinic resonances, H_{meso} 8.75 (s, 4 H), 8.66 (s, 2 H), biphenylene 7.15-6.65 (m, 6 H), CH_2CH_3 3.92 (m, 4 H), 3.71 (m, 4 H), 3.51 (m, 8 H), CH_3 3.28 (s, 12 H), 3.03 (s, 12 H), CH_2CH_3 1.70-1.60 (m, 24 H); imidazole resonances, para phenyl 6.29 (t, 2 H), meta phenyl 6.08 (t, 4 H), ortho phenyl 5.13 (d, 4 H), $H_{imidazole}$ 1.14 (s, 2 H), 1.04 (s, 2 H), *tert*-butyl -0.61 (s, 18 H).

(21) (a) Sellmann, D.; Brandl, A.; Endell, R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 1019-1020. (b) Sellmann, D.; Jödden, K. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 464-465. (c) Smith, M. R., III; Hillhouse, G. L. *J. Am. Chem. Soc.* **1988**, *110*, 4066-4068.

The Endocyclic Restriction Test: Experimental Evaluation of Transition-Structure Geometry for a Nucleophilic Displacement at Neutral Nitrogen

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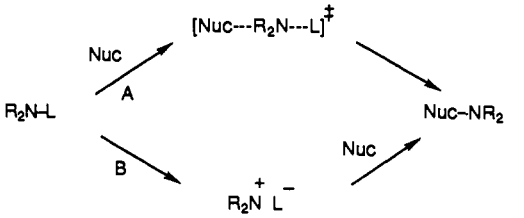
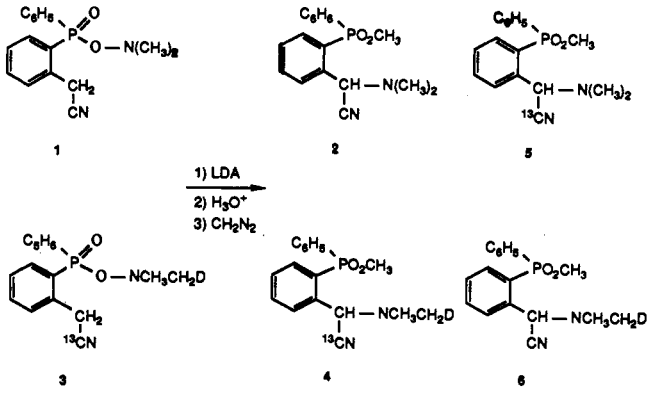
The mechanism of nucleophilic substitution at a formally neutral nitrogen atom is a matter of chemical and biochemical interest.[1-3] The limiting possibilities are shown in the first drawing as A a concerted reaction in which the transition structure has entering and leaving groups associated with nitrogen and B an ionization process involving the formation of an ion pair which is subsequently attacked by a nucleophile. Both reaction pathways are precedented in the literature.[2,3] In order to distinguish between these alternatives, we have evaluated the geometry of a nucleophilic substitution at a nitrogen bearing two methyl groups and addressed the possibility of reversible formation of an ion pair. The results, which provide the first experimental evidence for the geometry of a transition structure in a nucleophilic displacement at neutral nitrogen, are consistent with a concerted S_N2 mechanism.[3]



Suggestions of geometries for transition structures in substitutions at nonstereogenic atoms generally are made by analogy to formally similar processes at stereogenic atoms. The endocyclic restriction test, however, offers an experimental approach for evaluation of transition-structure geometries that is independent of the stereogenicity of the reaction center.[4,5] The work of Boche et al. which establishes that nucleophilic substitution occurs at the nitrogen of *N,N*-dimethyl-*O*-(diarylphosphinyl) derivatives allows application of this approach to a formally neutral nitrogen.[6] We have investigated the conversion of **1** to **2** which occurs in 11% yield on treatment of **1** with lithium diisopropylamide (LDA) in tetrahydrofuran followed by reaction with water, acidification, and treatment with diazomethane. If there is a geometrical requirement such that reaction cannot occur endocyclically within the confines of a six-membered ring, e.g., an S_N2 reaction, the reaction would occur intermolecularly. If reaction could occur within the confines of a formal six-membered ring, e.g., via an ion pair, the reaction could be intramolecular. A double labeling experiment was carried out with a mixture of **1** and **3** to distinguish the intermolecular and intramolecular pathways. For an intermolecular reaction the products would be **2**, **4**, **5**, and **6**, while an intramolecular reaction would give only **2** and **4**. The expectations for each possibility and the experimentally observed results of label scrambling which show that transfer of the dimethylamino group in the conversion of **1** to **2** is an intermolecular reaction are shown in Table I.[7] Recovered reactants were unscrambled, and a control experiment established that scrambling of the label in the products does not occur under these conditions.



(1) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947. Famulok, M.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 468. Singer, B.; Kusmierek, J. T. *Annu. Rev. Biochem.* **1982**, *51*, 655. Lai, C. C.; Miller, E. C.; Miller, J. A.; Leim, A. *Carcinogenesis* **1987**, *8*, 471.

(2) For discussion of aromatic nitrenium ions, see: Panda, M.; Novak, M.; Magonski, J. *J. Am. Chem. Soc.* **1989**, *111*, 4524. Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498 and references cited therein.

(3) For discussions of S_N2 substitutions at nitrogen, see: (a) Ulbrich, R.; Famulok, M.; Bosold, F.; Boche, G. *Tetrahedron Lett.* **1990**, *31*, 1689. (b) Novak, M.; Martin, K. A.; Heinrich, J. L. *J. Org. Chem.* **1989**, *54*, 5430. (c) Yamamoto, F.; Oae, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 77 and references cited therein.

(4) For seminal reports, see: Tenud, L.; Farooq, S.; Seible, S.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059. Hogg, D. R.; Vipond, P. W. *J. Chem. Soc. C* **1970**, 2142.

(5) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016. That work addresses the question of the geometry of displacement at a formally negative nitrogen of a lithium alkoxyamide by an organolithium reagent, and we have suggested that lithium bridging is a critical feature which brings the reactive components together for an S_N2 transition structure.[3] The present results in which the displacement occurs at a formally neutral nitrogen may be considered more general in revealing the favored geometry of nucleophilic substitution at a nitrogen.

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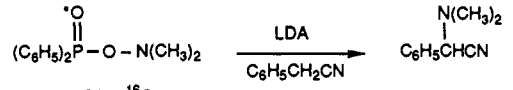
Table I. Isotropic Ratios for the Conversion of a Mixture of **1** and **3** to **2**, **4**, **5**, and **6**

mixture	M[a,b]	M + 1[a]	M + 2[a]
1 and **3**	60	4	37
2, **4**, **5** and **6**	40	47	14
intermolecular reactn[c]	38	48	15
intramolecular reactn[c]	60	4	37

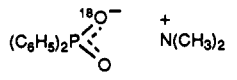
[a] Determined by FIMS (±5%). [b] Molecular ion for ^{12}C, ^{1}H compound. [c] Calculated on the basis of the mixture of **1** and **3**.

If the reaction were to involve an ion pair, the intermolecular result could be consistent with nucleophilic addition occurring on the side of the ion pair opposite the phosphinate leaving group. The second-order kinetics observed by Boche for similar reactions would require the ion pair to be formed reversibly.[3a] The work of Goering suggests that such an ion pair that reacts with an external nucleophile would be symmetrical by the criterion of scrambling of the oxygen atoms.[8] We have evaluated the possible intermediacy of a symmetrical ion pair from **7** in its reaction with benzyl cyanide and LDA to give **8** in 65% yield by the use of the ^{18}-O-labeled derivative **9**. If the reaction involved a reversibly formed symmetrical ion pair **10**, we would expect the ^{18}O label in **9** to be scrambled between the two oxygens of recovered reactant. However, we find that recovered **9** from a reaction that has proceeded to 80% completion has the ^{18}O label unscrambled. The position and extent of the label were established by reaction of **9** with phenyllithium, a substitution at phosphorus that gives triphenylphosphine oxide, which was found to have the same level of ^{18}O from both initial and recovered **9**. If scrambling had occurred, the triphenylphosphine oxide from recovered **9** would have been one-half of that from the initial **9**, in contrast to our observation.



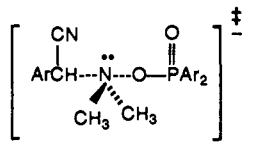
7, *O = ^{16}O
9, *O = ^{18}O

8



10

The present results show that the displacement at the nitrogen of a dimethylamino group of an oxygen of a phosphinate by an anionic carbon cannot be achieved within the endocyclic confines of a six-membered ring and that the reaction does not involve internal return from a symmetrical ion pair. We suggest that nitrogen transfer occurs in a concerted reaction with the transition-structure geometry of a trigonal bipyramid shown for **11**. In this transition structure the entering and leaving groups are at a large angle analogous to that of a classic S_N2 displacement and consistent with the mechanism proposed by Boche for this reaction.[3a] This provides, to the best of our knowledge, the first experimental information about the geometry of nucleophilic displacement at a formally neutral nitrogen atom.[5] We also note that this work further illustrates the value of the endocyclic restriction test for an experimental evaluation of transition-structure geometry to allow a choice between alternative reaction mechanisms.[9]



11

Acknowledgment. We are grateful to the National Science Foundation and National Institutes of Health for support of this work.

(6) (a) Boche, G.; Bosold, F.; Niessner, M. *Tetrahedron Lett.* **1982**, *23*, 3255. (b) Boche, G.; Schrott, W. *Tetrahedron Lett.* **1982**, *23*, 5403. (c) Boche, G.; Sommerlade, R. H. *Tetrahedron* **1986**, *42*, 2703.

(7) This reaction was carried out to 10% completion because on longer reaction times label scrambling was observed in the reactant.

(8) For related cases using this approach for carboxylates, see: Scott, C. M.; Underwood, G. R.; Kirsch, R. B. *Tetrahedron Lett.* **1984**, *25*, 499. Goering, H. L.; Levy, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 120. **Note Added in Proof**: For a recent discussion of ^{18}O scrambling in a sulfonate ester see: Dietze, P. E.; Wojciechowski, M. *J. Am. Chem. Soc.* **1990**, *112*, 5240.

(9) For another recent use of this approach and leading references, see: Beak, P.; Allen, D. A.; Lee, W. K. *J. Am. Chem. Soc.* **1990**, *112*, 1629.

Bile Salt Modulated Stereoselection in the Cholesterol Esterase Catalyzed Hydrolysis of α-Tocopheryl Acetates[1]

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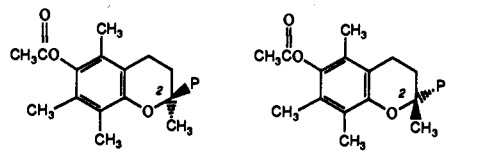
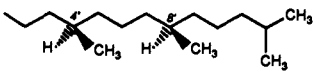
A major characteristic of catalysis by enzymes is stereoselectivity[3] which can be modified by changing the precise structure of the active site. In principle, this can be achieved by exotic procedures such as "protein engineering",[4] or by the simple expedient of changing the reaction medium,[5] or by unfolding and then refolding the enzyme.[6] The potential impact of an altered enzymic stereoselectivity on organic syntheses and mechanistic biochemistry has greatly encouraged research on this topic. While attempting to reconcile differences between the in vivo[7] and in vitro[8] rates of the carboxylic ester hydrolase (EC 3.1.1.13) catalyzed hydrolysis of (2*R*,4′*R*,8′*R*)- and (2*S*,4′*R*,8′*R*)-α-tocopheryl acetates (*RRR*- and *SRR*-α-TAc)[9] in the presence of the obligatory 3α,7α,12α-trihydroxy bile salts,[10] cholate, taurocholate, and glycocholate, we made the novel discovery that *the structure of the bile salt also has a profound effect on the stereoselectivity of this reaction.*

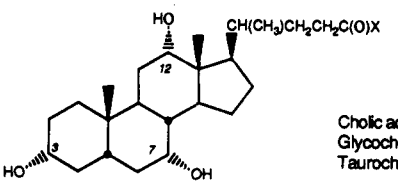


2*R*, 4′*R*, 8′*R*-α-tocopheryl acetate

2*S*, 4′*R*, 8′*R*-α-tocopheryl acetate



P (phytyl tail)



X	
Cholic acid	OH
Glycocholic acid	$NHCH_2CO_2H$
Taurocholic acid	$NHCH_2CH_2SO_3H$

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‡ Institute for Biological Sciences.

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