

[poly(dGdC)]₂ was similar but the increase with CT DNA and decrease with [poly(dAdT)]₂ were somewhat smaller than for TθpyP. The viscosity results reinforce the conclusions that TθpyP and TMpyP(4) DNA binding modes are the same but suggest that the higher charge of TθpyP influences the hydrodynamic properties of the TθpyP-DNA adduct.

Although similar in size to TθpyP and identical in charge to TMpyP(4), TθOPP gave only a gradual decrease in SRV for CCS DNA (Figure 3) and for the linear polymers. Therefore, TθOPP does not intercalate. The TθOPP chromophore is rather different from any used in previous studies with DNA. However, with all three linear DNAs, a time-dependent formation of a large conservative CD signal was observed, and the Soret band was red shifted by 7 nm with 20–40% H. The largest CD signal was found with [poly(dAdT)]₂ (Figure 2, [θ]₄₂₄ = -2 × 10⁶ and [θ]₄₃₆ = 1.3 × 10⁶). This optical spectroscopic pattern for porphyrins, e.g., TMAP, has been attributed to highly organized outside self-stacking.^{13,15} In contrast to previous studies, where the conservative CD curves are induced only in high salt,¹³ TθOPP produces the same pattern in both high and low salt. Another difference is that the large CD signals often have been found primarily at a high R,¹³ but we find such signals at low R (even at 0.001) with TθOPP. At low R values some self-stacking porphyrins become intercalators.¹³ However, TθOPP does not intercalate because of the high electron density in the porphyrin core. Most porphyrins studied previously are rigid. The long flexible tentacle arms of TθOPP probably facilitate favorable outside self-stacking interactions while simultaneously permitting near-optimal electrostatic interaction with the DNA phosphate groups. In addition to extending the diversity of potential binding interactions between porphyrins and DNA, the results presented here provide clear evidence that porphyrin intercalation does not require planar traversing groups but does require an electron-deficient porphyrin core.

Acknowledgment. This work was supported by the National Institutes of Health Grant AI-127196.

The First Determination of Carbonyl Oxide Geometry. Effect of Ring Size on the Stereochemistry of Carbonyl Oxides from Ozonolysis of Cycloalkenes

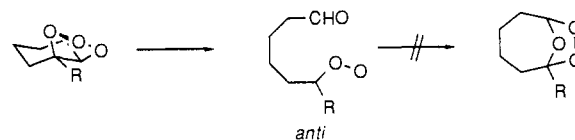
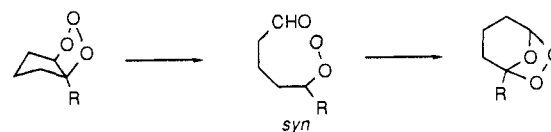
William H. Bunnelle* and Sang-ge Lee

Department of Chemistry
University of Missouri
Columbia, Missouri 65211

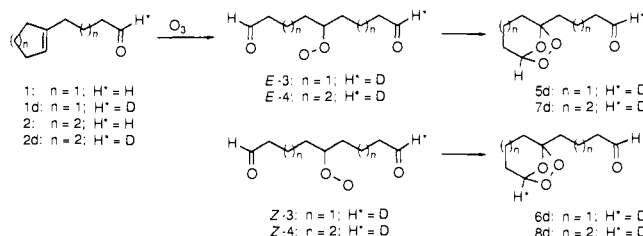
Received June 17, 1992

The stereochemistry of 1,2,4-trioxolanes (final ozonides) produced during ozonolysis depends on the geometry of the starting alkene, a result which requires that the intermediate carbonyl oxide is also formed with some stereospecificity.¹ Refinements of the basic Criegee mechanism, which incorporate carbonyl oxide stereoisomerism and can account for the overall stereochemistry of the ozonide formation, have been proposed,² but the predictions for carbonyl oxide geometry have not been verified experimentally. The problem is that the final ozonide stereochemistry depends on the combination of the geometry of the carbonyl oxide with the endo-exo topography of its cycloaddition with a carbonyl group. Therefore, deduction of the carbonyl oxide stereochemistry from that of the final ozonide requires knowledge of the particular

Scheme I



Scheme II



cycloaddition transition state, and vice versa.

It occurred to us that this ambiguity could be resolved in the case of intramolecular cycloaddition of a carbonyl oxide. Basically, intramolecular ozonide formation can occur only if the carbonyl oxide has the syn geometry with respect to the tethered carbonyl trap. If the carbonyl oxide stereochemistry is anti, a concerted, intramolecular cycloaddition is sterically impossible, provided that the tether is relatively short (two to four atoms). In this way, the extent of intramolecular trapping can be related to the carbonyl oxide geometry.³ We now report our initial results, which indicate that intramolecular ozonide formation is indeed highly sensitive to carbonyl oxide stereochemistry.

We chose as a test system the ozonolysis of 1-alkylcyclopentenes and -cyclohexenes. It is well established that cyclopentenes form ozonides in fair to excellent yields (50–90%).⁴ This implies that the carbonyl oxide is formed (largely) with a geometry syn to the cognate carbonyl group, so that intramolecular cyclization is facile. Consistent with this idea, semiempirical calculations indicate that the lowest-energy conformation for the primary ozonide of cyclopentene has the 1,2,3-trioxolane ring in an endo-folded envelope.⁵ A least-motion fragmentation² from this structure would lead to the syn-oriented carbonyl oxide (Scheme I).

On the other hand, the conformation of the primary ozonide of a 1-alkylcyclohexene should be determined largely by the preference for a chair conformation for the six-membered ring with the alkyl substituent in an equatorial orientation. The fused trioxolane ring must then span vicinal axial and equatorial positions, and preferred fragmentation to place the carbonyl oxide on the alkyl-substituted carbon will produce the anti carbonyl oxide, which cannot cyclize intramolecularly. Indeed, cyclohexenes are notorious for producing only minuscule yields of monomeric ozonides, instead forming oligomeric peroxides by intermolecular reaction.⁶ This is usually attributed to unfavorable entropy effects in the intramolecular cyclization of the carbonyl oxide-aldehyde pair from a cyclohexene. While that may be a contributing factor,

(3) This is, in essence, an application of the endocyclic restriction test; cf.: Beak, P. *Acc. Chem. Res.* 1992, 25, 215–222.

(4) (a) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1, pp 78–82. (b) Bunnelle, W. H.; Isbell, T. A. *J. Org. Chem.* 1992, 57, 729–740.

(5) Semiempirical calculations with Dewar's Austin model 1 (AM1)^{5a} or Stewart's parametric model 3 (PM3)^{5b} parameter sets were carried out using the program Mopac:^{5c} (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* 1985, 107, 3902–3909. (b) Stewart, J. J. P. *J. Comput. Chem.* 1989, 10, 221–264. (c) Stewart, J. J. P. QCPE 455, Vax/VMS Version 5.0.

(6) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1, p 87.

(1) Bauld, N. A.; Thompson, J. A.; Hudson, C. E.; Bailey, P. S. *J. Am. Chem. Soc.* 1968, 90, 1822–1830.

(2) (a) Bailey, P. S.; Ferrell, T. M. *J. Am. Chem. Soc.* 1978, 100, 899–905. (b) Lattimer, R. P.; Kuczkowski, R. L.; Gillies, C. L. *J. Am. Chem. Soc.* 1974, 96, 348–358. (c) Kuczkowski, R. L. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 197–276. (d) Cremer, D. *J. Am. Chem. Soc.* 1981, 103, 3619–3626. (e) Cremer, D. *J. Am. Chem. Soc.* 1981, 103, 3627–3633. (f) Cremer, D. *Angew. Chem., Int. Ed. Engl.* 1981, 20, 888–889.

we suggest that the low yield of ozonide is due to the fact that the anti carbonyl oxide cannot cyclize intramolecularly, and so intermolecular reaction (oligomerization) competes successfully.

To test this, we designed the deuterium-labeled substrates **1d** and **2d** (Scheme II). Ozonation of each of these proceeds to a quasi-symmetrical intermediate, in which the geometry of the carbonyl oxide is differentiated only by the isotope label on the tethered aldehydes. Since the kinetic secondary isotope effect for cyclization of the carbonyl oxide with unlabeled vs labeled aldehyde is quite small,⁷ any selectivity in this process, as measured by the ratio of isotopomeric ozonides, must be attributed to the carbonyl oxide geometry.

The requisite aldehydes were prepared by reduction of the corresponding esters,^{8,9} a route which can be modified to produce either the labeled or unlabeled systems. Ozonolysis of **1** (pentane, -78 °C) provided a 50% yield of the ozonide **5**, after chromatography. This product was characterized by signals in the ¹H NMR at 9.77 ppm (t, *J* = 1.4 Hz) and 5.76 (br s) for the aldehyde and ozonide bridgehead protons, respectively. Repetition of the experiment, using labeled aldehyde **1d**, provided a comparable yield of a mixture of ozonide isotopomers **5d** and **6d**, in a ratio of 8:1, respectively, as determined by NMR integration. This regioselectivity for the cyclization indicates clearly that there is a strong preference for cyclization of the carbonyl oxide with the newly formed aldehyde, in accord with the prediction that **1d** will lead preferentially to carbonyl oxide (*E*)-**3**.

Ozonolysis of cyclohexene **2** under the same conditions provided a 67% yield of the monomeric ozonide **7**. The structure of **7** was confirmed by spectroscopic analysis, including the characteristic ¹H NMR signals at 9.77 (br s) and 5.62 ppm. This remarkably high yield of ozonide stands in contrast to the results obtained with other cyclohexenes and suggests that formation of cyclohexene ozonide is not limited by entropic factors. Finally, when the labeled substrate **2d** was treated with ozone, the monomeric ozonide was found to consist of the isotopomers **7d** and **8d** in a ratio of 1:23. The very high selectivity for cyclization of the carbonyl oxide to the deuterated aldehyde is convincing evidence that the carbonyl oxide has the geometry represented in (*Z*)-**4**, in accord with predictions based on the conformation of the primary ozonide.

These experiments provide the first straightforward assessment of the stereochemistry of carbonyl oxide intermediates. Clearly, the highly regioselective reaction from each of the cycloalkene precursors demonstrates that the carbonyl oxide is formed with good stereoselectivity and that the stereochemical integrity of this intermediate is maintained.¹⁰ Likewise, the relationship of cyclization pathway to carbonyl oxide geometry is that expected for a concerted cycloaddition pathway. Most importantly, these results establish the viability of intramolecular trapping for assignment of carbonyl oxide geometry. Further applications of this method are in progress and will be reported in due course.

Acknowledgment. We thank the National Science Foundation (CHE 9108712) for support of this project, as well as for the support of the NMR facilities (CHE 89-08304) used in this work.

Supplementary Material Available: ¹H NMR spectra for **1**, **1d**, **2**, **2d**, and their ozonolysis products (8 pages). Ordering information is given on any current masthead page.

(7) (a) Kuczkowski, R. L. *Acc. Chem. Res.* **1983**, *16*, 42-47. (b) Fong, G. A.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 4763-4768. (c) Choe, J.-I.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 4839-4841. (d) Choe, J.-I.; Painter, M. K.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 2891-2895.

(8) (a) Ruppert, J. F.; White, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 1808-1813. (b) Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem.* **1972**, *25*, 1081-1105.

(9) The aldehydes were invariably contaminated with the isomeric, exocyclic alkenes. These gave different products on ozonolysis and did not interfere with the isotopomer assay.

(10) (a) Cremer, D. *J. Am. Chem. Soc.* **1979**, *101*, 7199-7205. (b) Keul, H.; Kuczkowski, R. L. *J. Org. Chem.* **1985**, *50*, 3371-3376. (c) Wojciechowski, B. J.; Pearson, W. H.; Kuczkowski, R. L. *J. Org. Chem.* **1989**, *54*, 115-121.

The Temporary Silicon Connection in the Control of the Regiochemistry of 4 + 2 Cycloadditions

Gilbert Stork,* Tin Yau Chan, and Gloria A. Breault

Department of Chemistry
Columbia University
New York, New York 10027

Received June 19, 1992

The "temporary silicon connection" achieves the regioselective, and often stereoselective, formation of carbon-carbon bonds by temporarily bringing together two reaction partners by means of an eventually removable silicon atom. During the last few years we have investigated the usefulness of that concept in a variety of ionic, radical, photochemical, and cycloaddition processes.¹ This communication is concerned with 4 + 2 cycloadditions.

Scheme I illustrates the process in a simple case. In this prototypical case, the overall reaction **1** → **4**[†] is equivalent to the addition of ethylene, acting as a dienophile, to diene **1**. No question of regiochemistry arises in this case when the silicon is simply removed from the adduct, but even in this simple case, the regiochemistry implicit in the process is brought forth when the silicon atom is replaced by a hydroxyl, as in **1** → **5**. The regiocontrol which results when substituted ethylenes are used in the temporary silicon connection process is illustrated by the transformation of **6**[‡] to **7**.⁹ (Scheme II).

Scheme III illustrates some of the numerous cyclizations involving vinylsilanes which we have investigated. The formation of **15**¹⁰ is notable in that it involves addition to a 1,1-disubstituted diene, a type of substitution which would not be expected to be productive in a bimolecular mode.

The effective use of silicon-tethered simple alkenes as dienophiles augured well for the use of more typical dienophiles such as acrylic esters as partners in the silicon-tethered Diels-Alder

(1) Inter alia, see: (a) Keitz, P. Ph.D. Thesis, Columbia University, 1988. (b) Lambert, P. Ph.D. Thesis, Columbia University, 1991. (c) Stork, G. *Abstracts of 32nd National Organic Chemistry Symposium*; Organic Chemistry Division, ACS, 1991; p 115. (d) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054. (e) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087. For internal 4 + 2 additions in which the silicon connection involves oxygen atoms, see: Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, *33*, 4073 and references therein.

(2) All 4 + 2 cycloaddition reactions were carried out in benzene solutions in sealed tubes. They can also be performed in solvents (chlorobenzene, anisole, ...) of suitable boiling points.

(3) Use of vinyl(diphenyl)chlorosilane instead of the dimethyl analog gave very similar results.

(4) The structures of the various cycloadducts were established by ¹H NMR and NOE measurements.

(5) Most of the silylated derivatives of sorbyl alcohol were made by reaction of the required alkenyl Grignard or lithium derivative with (*N,N*-dimethylamino)dimethylchlorosilane, followed by reaction of the resulting (*N,N*-dimethylamino)alkenylsilane with **1**.⁶

(6) Stork, G.; Keitz, P. *Tetrahedron Lett.* **1989**, *30*, 6981.

(7) Replacement of the carbon-silicon bond by a carbon-hydrogen bond (hydrodesilylation) has been shown⁸ to require the presence in the substrate of a hydroxyl substituent capable of forming a ring (no larger than five-membered) with the silicon atom (cf. **3** → **4**), a condition which is a corollary of the presence of an allylic hydroxyl in the original diene (e.g., **1** in this work). The fluoride-induced hydrodesilylations referred to in this communication presumably involve carbanion or radical intermediates, and there is, therefore, no correspondence between the stereochemistry of the intermediate siloxane adducts and that of their desilylation products. In contrast, the transformation of the carbon-silicon into a carbon-oxygen bond by reaction with various peroxides takes place with retention of configuration (essentially a Baeyer-Villiger reaction).⁹ Thus, in addition to leading to regioselective formation of hydroxycyclohexenes, replacement of the silicon by a hydroxyl gives ratios of epimeric alcohols which correspond to the stereochemistry of their silane precursors, presumably reflecting the partition between endo and exo transition states in the 4 + 2 cycloadditions.

(8) Hudrlík, P. F.; Hudrlík, A.; Kulkarni, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 6809.

(9) (a) Tamao, K.; Akita, H.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. (b) Fleming, I.; Henning, R.; Plant, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29.

(10) The structure was established by conversion to the corresponding 1,2,4-trimethylcyclohexanes (Pd-H₂; TsCl-pyridine; LAH) and comparison with authentic, stereodefined samples (from Wiley Organics, Coshocton, OH).