VOLUME 20 NUMBER 8
ACCOUNTS OF CHEMICAL RESEARCH
AUGUST, 1987

Registered in U.S. Patent and Trademark Office; Copyright 1987 by the American Chemical Society

Cation Radical Catalyzed Chain Oxygenation of Alkylated Olefins and Dienes

STEPHEN F. NELSEN

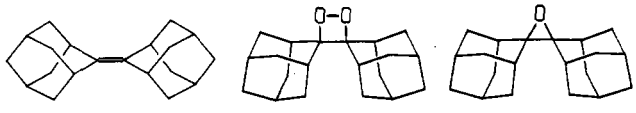
S. M. McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received August 19, 1986 (Revised Manuscript Received April 28, 1987)

Introduction

The role of cation radicals as intermediates in a variety of reactions of organic compounds is currently becoming more apparent, as detailed in recent reviews.[1] This Account focuses on a rather limited aspect of cation radical chemistry, the elucidation of cation radicals as chain-carrying intermediates in the reaction of some unsaturated hydrocarbons with dioxygen and the development of this chemistry into a preparatively useful method for making certain cyclic peroxides.

Biadamantylidene (**1**)[2] and its analogues have been of pivotal importance in the study of alkene reaction mechanisms because their Bredt's rule protected alkyl groups impose special geometrical constraints. In addition to the substantial bulk of the α-branched alkyl groups, the allylic hydrogens are held in the nodal plane of the olefinic p orbitals, inhibiting allylic C–H cleavage by any mechanism. Most oxygenating conditions convert **1** to mixtures of its remarkably stable[2b-d] dioxetane (**2**) and epoxide[2e] (**3**). Photolysis with sensitizers which produce $^1O_2$ give **2**/**3** ratios which depend on the sensitizer used as well as on other conditions,[3] although **2** appears to be the only product derived from $^1O_2$. The possibility of cation radical intermediates in some photooxygenation reactions was suggested by Bartlett in a review,[4] in which he mentioned work with M. J. Shapiro where the one-electron oxidant (p-Br-$C_6H_4)_3N^{\bullet+}$ ($\mathbf{4}^{\bullet+}$) produced **2** without giving any **3** and suggested that the Barton group's work on the diene to endoperoxide conversion using $^3O_2$[5] might also be rationalized as proceeding through cation radicals. Schaap and co-workers[6] demonstrated a nonsinglet oxygen pathway from **1** to **2** in the 9,10-dicyanoanthracene sensitized photooxygenation, in which $\mathbf{1}^{\bullet+}$ reacts with $O_2^{\bullet-}$ generated from the sensitizer radical anion to give **2**, as previously found in similar reactions on other systems.[7] The fact that electron-transfer quenching of cation radicals by $O_2^{\bullet-}$ generates $^1O_2$, which gives the same product, makes this reaction difficult to quantify. In contrast, Akaba and co-workers have shown that photolysis of **1** and tetracyanoethylene



1 2 3

Stephen F. Nelsen, born in Chicago in 1940, received his B.S. degree from the University of Michigan and his Ph.D. from Harvard University. He joined the faculty at the University of Wisconsin in 1965, where he is now professor.

(1) (a) For a general review, see: Hammerich, O.; Parker, V. D. *Adv. Phys. Org. Chem.* **1984**, *20*, 55–189. (b) On some hydrocarbon cation radicals, see: Courtneidge, J. L.; Davies, A. G. *Acc. Chem. Res.* **1987**, *20*, 90–97. (c) On proton-transfer reaction of photogenerated ion pairs, see: Lewis, F. D. *Ibid.* **1986**, *19*, 401–405.

(2) (a) Strating, J.; Wieringa, J. H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1969**, 907. (b) Wieringa, J. J.; Strating, J.; Wynberg, H.; Adam, W. *Tetrahedron Lett.* **1972**, 169. (c) Schuster, G. D.; Turro, N. J.; Steinmetzer, H.-C.; Schaap, A. P.; Faler, G.; Adam, W.; Lu, J. C. *J. Am. Chem. Soc.* **1975**, *97*, 7110. (d) Hess, J.; Vos, A. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1977**, *B33*, 3527. (e) Wynberg, H.; Boelema, F.; Wieringa, J. H.; Strating, J. *Tetrahedron Lett.* **1970**, 3613.

(3) (a) Schaap, A. P.; Faler, G. R. *J. Am. Chem. Soc.* **1973**, *95*, 3381. (b) Bartlett, P. D. *Chem. Soc. Rev.* **1976**, *5*, 154. (c) Jefford, C. W.; Boschung, A. F. *Tetrahedron Lett.* **1976**, 4771. (d) Jefford, C. W.; Bartlett, A. F. *Helv. Chim. Acta* **1977**, *60*, 2073.

(4) Bartlett, P. D. *ACS Symp. Ser.* **1978**, *No. 69*, 15–32.

(5) Barton, D. H. R.; LeClerc, G.; Magnus, P. D.; Menzies, I. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2055.

(6) (a) Schaap, A. P.; Zaklika, K. A.; Kaskar, B.; Fung, L. W.-M. *J. Am. Chem. Soc.* **1980**, *102*, 389. (b) Akaba, R.; Sakuragi, H.; Tokumaru, K. *Tetrahedron Lett.* **1981**, *25*, 665.

(7) (a) Eriksen, J.; Foote, C. S.; Parker, T. L. *J. Am. Chem. Soc.* **1977**, *99*, 6455. (b) Eriksen, J.; Foote, C. S. *J. Phys. Chem.* **1978**, *82*, 2659. (c) Spada, C. T.; Foote, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 391. (d) Manring, L. E.; Eriksen, J.; Foote, C. S. *Ibid.* **1980**, *102*, 4275. (e) Eriksen, J.; Foote, C. S. *Ibid.* **1980**, *102*, 6083. (f) Zalika, K. A.; Kashar, B.; Schaap, A. P. *Ibid.* **1980**, *102*, 386.

0001-4842/87/0120-0269$01.50/0 © 1987 American Chemical Society

in $^3O_2$-saturated solvent gives principally **3**, as well as tetracyanoethylene epoxide.[8a] Even 20% trifluoroacetic acid has been shown to convert **1** and oxygen to mixtures of **2** and **3** in the dark.[8b]

Mechanism of Conversion of 1 to 2 by One-Electron Oxidants

The Bredt's rule protection of $1^{\bullet+}$ makes it unusually kinetically stable, allowing convenient electrochemical and spectral measurements on this cation radical.[9-11] Most notably, $1^{\bullet+}$ is purple[11] because it has an extremely broad absorption at 530 nm ($\epsilon > 970$), assigned to a transition from a σ orbital to the half-filled π orbital. $1^{\bullet+}$ and its analogues are the first compounds for which such a "hyperconjugation transition"[12] was authentically observed.

The fact that $1^{\bullet+}$ is sensitive to air was noted in the first ESR studies on this cation,[9] and the groups of Nelsen and Clennan simultaneously published[13] cyclic voltammetry studies demonstrating the chain nature of the reaction of $1^{\bullet+}$ with $^3O_2$. Most of the oxidation current observed for the reversible $1,1^{\bullet+}$ couple disappears when the solvent is saturated with oxygen and the falloff in current past the peak potential is much faster than exponential. This behavior shows that a reaction product of $1^{\bullet+}$ with $^3O_2$ is a better oxidant than $1^{\bullet+}$, causing EC backward E (ECbE) electrochemical behavior.[14] Coulometry for the electrochemical oxidation indicated chain lengths (moles of **2** formed per coulomb of electrons removed) up to 24, which decreased when the concentrations of either **1** or oxygen were decreased.[13b] Chemical initiation[13a] with $4^{\bullet+}$ gave only **2** (as reported previously[4]) in a catalytic but slow reaction. Ando and co-workers[15] compared the electrochemically initiated oxygenation reactions of **1** analogues with photooxygenations, obtaining chain lengths for electrochemical oxidation of **1** of up to 78. They showed that the electrochemical conditions gave double-bond rotation isomers of recovered olefin, as well as scrambled dioxetanes, in contrast to photooxygenations with either dye or easily reduced photosensitizers.

Although the electrochemical conversion of **1** to **2** is quite clean, the reaction is not very useful preparatively because of the necessity of running the electrolysis at rather low concentration and of separating the product from supporting electrolyte. Cyclic voltammetry showed that $E^{\circ\prime}$ for the $1,1^{\bullet+}$ electron transfer is 1.59 V vs. SCE at −78 °C,[16] indicating why $4^{\bullet+}$ is a poor chemical catalyst for the conversion of **1** to **2**; the $4,4^{\bullet+}$ $E^{\circ\prime}$ is 1.17 V vs. SCE under the same conditions, so the electron transfer to form $1^{\bullet+}$ is over 9 kcal/mol endothermic. The intensely green cation radical (*o*-, *p*-Br_2-$C_6H_3)_3N^{\bullet+}$, $5^{\bullet+}$, which like $4^{\bullet+}$ was first prepared by Walters and co-workers[17] but was first isolated by Schmidt and Steckhan,[18] has $E^{\circ\prime}$ of 1.66 V under the same conditions and proves to be a superior catalyst for oxygenation reactions of tetraalkylolefins. A second modification which improves the cation radical catalyzed chain (CRCC) oxygenation reaction is lowering the temperature. In methylene chloride, the chain length observed for the conversion of **1** to **2** is only about 10 at room temperature but increases to over 800 at −78 °C, greatly decreasing the amount of the catalyst required and simplifying product purification, making the CRCC oxygenation reaction preparatively useful.[19] Because $5^{\bullet+}$ reacts with oxygenated compounds (it may be quenched with ether), the key to obtaining good yields in these reactions is minimizing the contact time of the product with the initiator, which is easy to carry out because of the color change which signals completion of the reaction. Addition of the intensely green initiator $5^{\bullet+}$ to solutions containing **1** causes immediate fading of the green color and appearance of the purple color of $1^{\bullet+}$. When the **1** is all consumed, the green color of $5^{\bullet+}$ reappears, and the reaction mixture should be worked up immediately. The total time for conducting such a CRCC oxygenation reaction is only a few minutes.

There were three likely candidates for the chain-carrying oxidant generated from olefin cation radicals and $^3O_2$. A single C–O bond could be formed, producing the open β-peroxycarbenium ion $A^{\bullet+}$ (as suggested by Clennan and co-workers[13b]), two C–O bonds could be formed to the same oxygen atom, producing the perepoxide cation radical $B^{\bullet+}$ (suggested as an intermediate in certain photooxygenation reactions by Bartlett[4]), or two C–O bonds could be formed to different oxygens, producing the dioxetane cation radical $C^{\bullet+}$. The chain-carrying oxidant causing the ECbE electrochemical behavior is rather clearly the dioxetane cation radical $C^{\bullet+}$. The $C^{\bullet+}$ intermediate from **1**, $2^{\bullet+}$, can be

A^+ B^+ C^+

observed to build up in solution at low temperature in nonnucleophilic enough solvents. Experiments with Bredt's rule protected secondary and tertiary bicyclic peroxide cation radicals[20] have shown that some examples with five- and six-membered peroxide rings are long-lived in solution even at room temperature in methylene chloride containing trifluoroacetic acid and anhydride (TFA and TFAA), despite their high $E^{\circ\prime}$ values of over 2.2 V. Hammerich and Parker[21] showed that addition of TFA and TFAA both kinetically stabilizes aromatic cation radicals and allows cyclic vol-

(8) (a) Akaba, R.; Sakuragi, H.; Tokumaru, K. *Chem. Lett.* **1984**, 1677. (b) Akaba, R.; Sakuragi, H.; Tokumaru, K. *Tetrahedron Lett.* **1984**, *25*, 665.

(9) Nelsen, S. F.; Kessel, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 2503.

(10) (a) Gerson, S. F.; Lopez, J.; Akaba, R.; Nelsen, S. F. *J. Am. Chem. Soc.* **1981**, *103*, 6716. (b) Assignment of the two smallest splittings was made in ref 22.

(11) (a) Nelsen, S. F.; Teasley, M. F.; Kapp, D. L.; Kessel, C. R.; Grezzo, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 791. (b) Clark, T.; Teasley, M. F.; Nelsen, S. F.; Wynberg, H. *Ibid.*, in press.

(12) Olah, G. A.; Pittman, C. U., Jr.; Symons, M. C. R. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Interscience: New York, 1968; Vol. 7, pp 197–201.

(13) (a) Nelsen, A. F.; Akaba, R. *J. Am. Chem. Soc.* **1981**, *103*, 2096. (b) Clennan, E. L.; Simmons, W.; Almgren, C. W. *Ibid.* **1981**, *103*, 2098.

(14) Feldberg, S. W.; Jeftic, L. *J. Phys. Chem.* **1972**, *76*, 2439.

(15) (a) Ando, W.; Kabe, Y.; Takata, T. *J. Am. Chem. Soc.* **1982**, *104*, 7314. (b) Kabe, Y.; Takata, T.; Ueno, K.; Ando, W. *Ibid.* **1984**, *106*, 8174.

(16) Conditions: methylene chloride containing 0.1 M n-$Bu_4N^+ClO_4^-$ at a platinum disk electrode at −78 °C.

(17) Baker, T. N., III; Doherty, W. P., Jr.; Kelly, W. S.; Newmeyer, W.; Rogers, J. E., Jr.; Spaulding, R. E.; Walters, R. I. *J. Org. Chem.* **1965**, *30*, 3714.

(18) Schmidt, W.; Steckhan, E. *Chem. Ber.* **1980**, *113*, 577.

(19) Nelsen, S. F.; Kapp, D. L.; Teasley, M. F. *J. Org. Chem.* **1984**, *49*, 579.

(20) (a) Nelsen, S. F.; Teasley, M. F.; Kapp, D. L.; Wilson, R. M. *J. Org. Chem.* **1984**, *49*, 1845. (b) Nelsen, S. F.; Teasley, M. F.; Bloodworth, A. J.; Eggelte, H. J. *Ibid.* **1985**, *50*, 3299.

(21) (a) Hammerich, O.; Parker, V. D. *Electrochim. Acta* **1973**, *18*, 537. (b) Parker, V. D. *J. Am. Chem. Soc.* **1976**, *98*, 98.

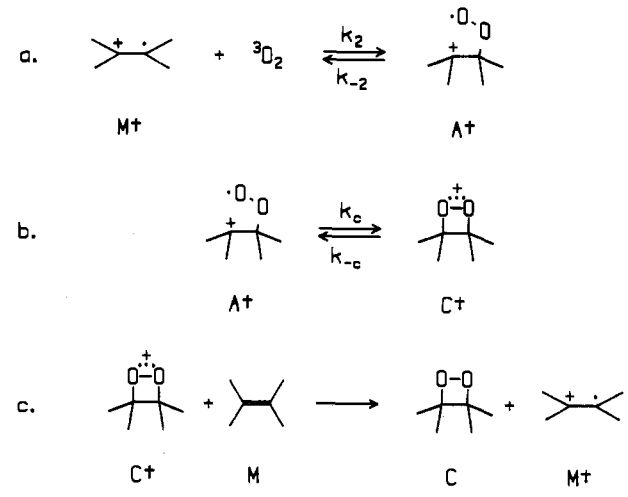
tammetry scans to much more positive potentials before substantial oxidation current is passed in a blank sample, apparently because of removing small amounts of basic impurities from the solvent. **2** gives a chemically reversible oxidation wave at −78 °C in 20:1:1 CH_2Cl_2/TFA/TFAA with a formal potential of 2.3 V vs. SCE, although the wave becomes completely irreversible at room temperature, where $\mathbf{2}^{\bullet+}$ does not survive for even a few milliseconds.[22] The same oxidation wave and ESR spectrum are produced by electrochemical oxidation starting with **2** or with **1** and oxygen.

The ESR spectrum of $\mathbf{2}^{\bullet+}$ is unexpectedly complex, but its splittings have been assigned by using deuteriated starting materials as 3.25 G (4 H, all H(γ) equatorial in the starting olefin) and 0.75 G (6 H, the other four H(γ) equatorial and two of the four near bridgehead H(β) hydrogens, one in each adamantane ring).[22] These assignments prove the equivalence of the two adamantane rings but demonstrate that the cation radical is twisted at the central CC bond and not equilibrating between the forms twisted in opposite directions on the ESR time scale. (Crystalline neutral **2** has been shown to be twisted by 26° by X-ray crystallography.[2d]) This requires assignment of the spectrum to $\mathbf{2}^{\bullet+}$ and not to an open form $A^{\bullet+}$ or the perepoxide cation radical $B^{\bullet+}$, which the low symmetry might have been interpreted to suggest in the absence of the labeling study.

Both the ESR work and the PE spectra of dioxetanes[22b] show that $\mathbf{2}^{\bullet+}$ has the three-electron π-bonded structure $C^{\bullet+}$ and not the alternative possibility of a long CC bond. $\mathbf{2}^{\bullet+}$ is not, however, the initial adduct of oxygen to $\mathbf{1}^{\bullet+}$. Bauld and co-workers have pointed out that cycloaddition of olefin cation radicals to several unsaturated systems ought to proceed one bond at a time,[23a] which is the result obtained by MNDO[23b] calculations for the reaction of ethylene cation with $^3O_2$. The perepoxide radical cation $B^{\bullet+}$ was calculated both to be quite unstable and to have high barriers for formation. Lower stability for $B^{\bullet+}$ than for $C^{\bullet+}$ is predicted because $C^{\bullet+}$ is stabilized by the presence of a 3e π bond. Compelling evidence for an open intermediate $A^{\bullet+}$ in CRCC oxygenation has been obtained by studying the double-bond rotation isomeric olefins *syn*- and *anti*-bi-8-bicyclo[3.2.1]octylidene, **6**[26a] (to be discussed in the next section).

The three-step chain shown in Scheme I therefore is proposed as the mechanism for the conversion of **1** to **2** in the presence of one-electron oxidants. The exothermicity for step c is simply the difference in $E^{\circ\prime}$ for $C,C^{\bullet+}$ and $M,M^{\bullet+}$, and electrochemical measurements at −78 °C have shown that step c is exothermic by over 15 kcal/mol, providing the driving force for the reaction.[22] Steps a and b cannot yet be separated quantitatively for mechanistic study because it has not proven possible to detect the open adduct $A^{\bullet+}$ either electrochemically or by ESR spectroscopy. If present in significant amount, $A^{\bullet+}$ must not be electroactive between 1.3 and 2.3 V vs. SCE. This cannot be used as evidence that $A^{\bullet+}$ does not build up, however, because it would not really be expected to be electroactive in this region.

Scheme I



Furthermore, as a peroxy radical with an exceedingly large alkyl substituent, very broad ESR lines would be expected,[24] so its detection by ESR would be expected to be prohibitively difficult.

Where $A^{\bullet+}$ reduces is a mechanistically significant point, because if the $A,A^{\bullet+}$ couple were positive of the $1,1^{\bullet+}$ couple, $A^{\bullet+}$ would be capable of carrying the kinetic oxygenation chain without closing to the dioxetane cation radical, as was suggested as the likely mechanism for the reactions in, for example, ref 1a. It seems to us very unlikely, however, that any example of $A^{\bullet+}$ would be a better oxidant than the olefin cation radical from which it is formed. In Hückel terms, the resonance integral β between the two p orbitals of an olefin stabilizes its bonding orbital relative to that of an isolated p orbital substantially. In the gas phase, the ionization potential for $(CH_3)_3C^{\bullet} \rightarrow (CH_3)_3C^+$ is 6.92 eV,[25] about 1.5 eV lower than that of $Me_2C{=}CMe_2$. We doubt that the effect of a β-peroxy substituent would raise the $A,A^{\bullet+}$ oxidation potential enough to overcome such a large difference, and therefore we believe that closure of $A^{\bullet+}$ to $C^{\bullet+}$ is necessary to carry the oxygenation chain shown in Scheme I and that $\mathbf{2}^{\bullet+}$ is the chain-carrying intermediate in the example under discussion.

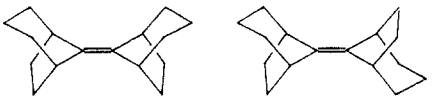
Electrochemical measurements have shown[27] that $\mathbf{2}^{\bullet+}$ is short-lived on the cyclic voltammetry time scale at room temperature and that its decomposition generates some $\mathbf{1}^{\bullet+}$. Simulations of the observed cyclic voltammogram showed that steps a and b must be an overall >2 kcal/mol endothermic under cyclic voltammetry conditions. The very exothermic electron transfer of step c therefore pulls the kinetic chain through the thermodynamically unfavorable equilibrium of steps a and b, allowing the reaction to proceed efficiently. A quantitative study of the cyclic voltammograms of **1** in 20:1:1 CH_2Cl_2/TFA/TFAA has allowed measurement of the rate constant for oxygen addition to $\mathbf{1}^+$, although steps a and b cannot be separated, so only the k_2' corresponding to $M^+ + O_2 \rightarrow C^{+}\bullet$ is available.[27] Simulations have shown that $k_2'[O_2]$ is about 42 s^- at room

(22) (a) Nelsen, S. F.; Kapp, D. L.; Gerson, F.; Lopez, J. *J. Am. Chem. Soc.* **1986**, *108*, 1027. (b) Nelsen, S. F. *J. Org. Chem.* **1984**, *49*, 1891.
(23) (a) Bauld, N. L.; Bellville, D. J.; Pabon, R.; Chelsky, R.; Green, G. *J. Am. Chem. Soc.* **1983**, *105*, 2378. (b) Chen, C.-C.; Fox, M. A. *J. Comput. Chem.* **1983**, *4*, 488.
(24) Thomas, J. R. *J. Am. Chem. Soc.* **1966**, *86*, 2063.
(25) (a) By PES: Houle, F. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 4067. (b) By electron impact: Lossing, F. B.; Semeluk, G. P. *Can. J. Chem.* **1970**, *48*, 955.
(26) (a) Nelsen, S. F.; Kapp, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 1265. (b) Nelsen, S. F.; Teasley, M. F. *J. Org. Chem.* **1986**, *51*, 3474.
(27) Nelsen, S. F.; Kapp, D. L.; Akaba, R.; Evans, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 6853.

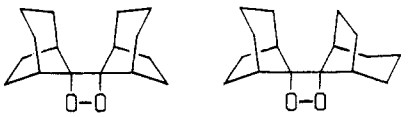
temperature and that $[O_2]$ under these conditions is 7.5 mM, so that k_2' is about 5600 M^{-1} s^{-1}. The reason for the large temperature effect observed on the chain length in chemically initiated CRCC oxygenations is probably that k_{-c} is >800 s^{-1} at room temperature and that $2^{\bullet+}$ gives other products besides $1^{\bullet+}$ upon its decomposition. At −78 °C, where $2^{\bullet+}$ lasts for seconds in the absence of reductants, even the rather low value of k_2' for $1^{\bullet+}$ is sufficient to carry an efficient oxygenation chain.

CRCC Oxygenation of Other Tetraalkylolefins

Significant information on the stereochemistry of the addition of oxygen to olefin cation radicals and their rotational barrier has come from studies on the oxygenation of the double-bond rotational isomers, *syn*- and *anti*-**6**.[26] Generation of *syn*-$6^{\bullet+}$ in the absence of



oxygen demonstrated that its barrier to rotation about the central CC bond is over 15.4 kcal/mol, and it undergoes oxygenation under CRCC conditions (where the cation radical lifetime is very short) to give only one of the possible syn dioxetanes, **7ee**. Thus, all of the

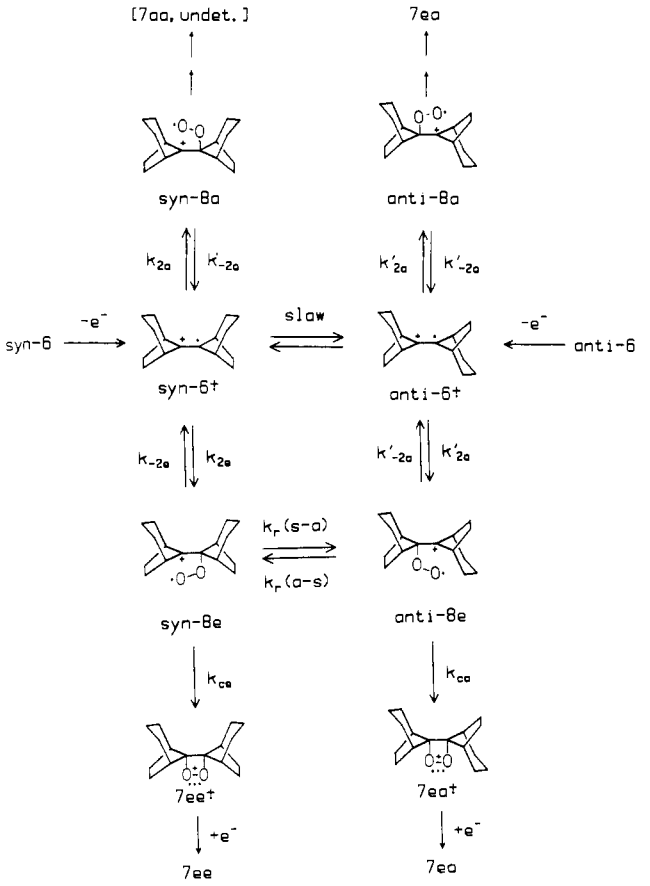


product involves attack of oxygen on *syn*-$6^{\bullet+}$ from the side opposite the $(CH_2)_3$ bridges, which we shall call equatorial attack; the stereoselectivity for the product of equatorial attack of O_2 must be at least 20:1. Although this is the sterically least hindered side, it should also be noted that it is also the side which leads to best electronic stabilization of the transition state for addition, since it places the three-carbon bridge anti to the entering nucleophile.[28]

Because the addition of O_2 to the olefin cation radical might be reversible, it is not clear whether the stereochemistry of the product formed is determined in the initial oxygen addition step or the closure to the dioxetane cation under our conditions, but preference for equatorial attack at C_7 of bicyclo[3.2.1]octane derivatives is well established.[28] In addition to the factors previously discussed for this phenomenon, the more recent suggestion by Verhoeven[29] that orbital symmetry differences between two- and three-carbon bridges are an important factor in determining σ assistance effects seems attractive to us. In contrast to the single dioxetane **7ee** obtained from *syn*-**6**, the anti isomer gave in addition to 80% of the anti dioxetane, **7ae**, 20% of **7ee**. The rotation about the central CC bond which allows **7ee** to be formed from *anti*-**6** has been shown not to occur at the olefin cation radical stage, and we believe that it must be occurring in an open intermediate $A^{\bullet+}$, which we will designate as **8**, with prefixes syn or anti

(28) (a) Foote, C. S.; Woodward, R. B. *Tetrahedron* **1964**, 687. (b) Grob, C. A.; Waldner, A.; Zutter, U. *Helv. Chim. Acta* **1974**, *67*, 717. (c) Sargent, G. D.; Mason, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 1063.
(29) Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 369.

Scheme II



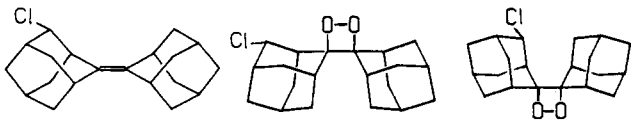
to indicate the rotational isomers about the central CC bond and suffixes a or e to indicate which face of the bicyclo[3.2.1]octyl system has the CO bond. Rotation about the central CC bond of the open intermediate must be slower than the second CO bond closure process (governed by k_c) to give only **7ee** from *syn*-**6** but competitive with closure for the isomer of **8** formed from *anti*-**6**, because dioxetanes with both syn and anti relationships between the bicyclo[3.2.1]octyl systems are isolated. The reactions involved are shown in Scheme II.

The closure (k_c) and electron-transfer steps are written as irreversible, which is experimentally true under our reaction conditions (−78 °C). The order of addition did not change the dioxetane product ratio from *anti*-**6**, although the concentration of reductants available for the final electron transfer averages about 10 times less when the olefin is added to the oxidant and would have led to a different product ratio if reversal of these steps had been significant. If these steps are irreversible as written, whether or not bond rotation will be observed in dioxetane products will depend only on the ratio of closure to rotation rates. We doubt that k_r(e–a) would differ significantly from k_r(a–e), because their transition states are the same, and *syn*- and *anti*-**8** differ little sterically. We must, however, expect different closure rates, because as stated above, nucleophiles have always been observed to react faster at the equatorial face than the axial face at position 7 of bicyclo[3.2.1]octane derivatives. If k_{ce}/k_{ca} were >5, the observed result would occur, but this is only a lower limit.

The results above on the stereochemistry of dioxetane formation from the isomers of **6** require an open in-

termediate we identify with $A^{\bullet+}$ which exhibits closure to the dioxetane competitive with central bond rotation for the isomer which closes more slowly. Because we have not been able to observe $A^{\bullet+}$ spectroscopically, we have no experimental evidence on possible interaction between the oxygens and the carbocationic center. Observing CC rotation competitively with closure to $C^{\bullet+}$ implies that such interaction is not particularly strong. Trapping of $A^{\bullet+}$ from **1** by $NO^{\bullet}$ [13] and by tetracyanoethylene radical anion[8a] has been suggested to explain formation of **3** with NO^+ and TCNE photostimulated initiation. Under conditions where the chain length for conversion of **1** to **2** is greater than 800, additive of several molar equivalents of 1,4-cyclohexadiene or 9,10-dihydroanthracene reduces the chain length for **1** consumption to less than 1.5 and causes epoxide **3** to become a major product, which also seems most easily explained by postulating trapping of $A^{\bullet+}$.[26b]

Additional evidence for the importance of σ participation effects in determining the rate of addition of O_2 to olefin cation radicals has come from cyclic voltammetry simulations of the ECbE wave of **1** and other olefins at −78 °C.[27] Steric hindrance is a major factor in determining the rate of addition, k_2', and *syn*- and *anti*-**6** are unquestionably less sterically hindered for oxygen attack than is **1**, yet both cation radicals give k_2' values only 0.13 times as large as that of $1^{\bullet+}$. 4-(e)-Cl-1, **9**, must closely resemble **1** sterically, yet its cation radical has a k_2' value is only 0.4 times that of $1^{\bullet+}$. Dioxetanes **10** and **11** are formed in a 25:1 ratio,[27]



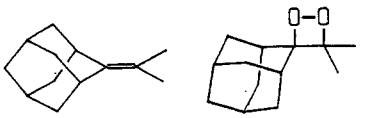
9 10 11

so there is a strong selectivity for attack syn to the chlorine bearing carbon over that from the opposite face of the double bond, which can only be reasonably rationalized as an electronic effect. The selectivity for CRCC dioxetane formation from **9** is in the same direction as for singlet oxygen attack but is significantly higher, as the product ratio for singlet oxygen attack is 3.1:1 at room temperature,[30] although some of the increase in selectivity is probably due to the temperature difference. As for the experiments on **6**, the stereochemistry of CRCC dioxetane formation from **9** is consistent with oxygenation from the side opposite the alkyl groups which best stabilize positive charge. It should be noted that addition of oxygen to an olefin cation radical increases charge density at the carbon which does not become bonded to oxygen, and both carbons are therefore formally oxidized in $A^{\bullet+}$ formation. It is reasonable that oxygenation would favor having the best cation-stabilizing alkyl groups anti to the CO bonds being formed, where they can best stabilize the transition state.

Dioxetane formation from alkylated olefins and singlet oxygen requires that the ene reaction, which produces allylic hydroperoxides by cleavage of a C_α–H bond, be geometrically inhibited.[31] One of the clearest examples of this requirement is in the singlet oxygenation of **12**, studied by Kellog and Kaiser.[31b] Although

12 13

the principal product is ene attack from the lower face in the view shown, peroxide cleavage followed by chromatographic separation allowed isolation of 5–10% of **13**, which clearly arises by $^1O_2$ attack from the more hindered, upper face, from which ene reaction cannot occur because the syn C–H bonds are required to be equatorial, and thus lie near the nodal plane of the π bond. Experiments with isopropylideneadamantane (**14**) have shown that ene products are not formed under



14 15

CRCC conditions even when methyl groups are directly attached to the double bond, so C_α–H cleavage is not sterically inhibited.

$14^{\bullet+}$ is far less kinetically stable than $1^{\bullet+}$, and both acidic solvent and low temperature are required to see any reversibility for **14** oxidation by cyclic voltammetry.[19] ECbE electrochemistry was observed under oxygen, but k_2 was so fast that we could not measure it by cyclic voltammetry, indicating that the great steric hindrance of **1** is important in causing the rather low k_2 value observed. When $5^{\bullet+}$ was used as oxidant, a chain length of about 60 was observed for formation of **15** in CH_2Cl_2 at −78 °C, and the yield of **15** isolated was 82%. Singlet oxygen gave only the allylic hydroperoxide, and although Adam and Encarnacion[32] were able to convert it to the bromodioxetane, they were unable to reduce off the bromine without destroying the dioxetane ring or to make **15** by Kopecky's method.[33]

It might be argued that CRCC oxygenation of **14** is not a fair test to see whether Bredt's rule protecting groups are required to obtain dioxetane formation, because the reaction goes through open intermediate $A^{\bullet+}$, and both steric and electronic effects will favor initial C–O bond formation to the CMe_2 carbon, which would make the intermediate still in fact Bredt's rule protected by the adamantyl system. We therefore next investigated[34a] oxygenation of dimethylhomoadamantene (**16**), which can only give an unprotected $A^{\bullet+}$. **16** showed ECbE electrochemistry, and interestingly, the chain length for **16** consumption was found to increase tenfold, from 5 to 50 (which is comparable to that for **14**), when the solvent for the CRCC reaction was changed from pure CH_2Cl_2 to the 20:1:1 acidic mixture. We presume that removal of basic impurities

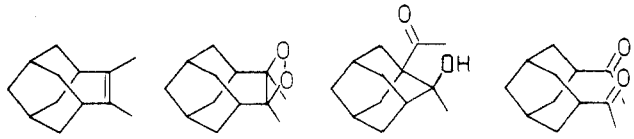
(30) (a) Wynberg, H.; Meijer, E. W.; Hummelen, J. C. In *Bioluminescence and Chemiluminescence*; Deluca, M. A., McElroy, W. D., Eds.; Academic: New York, 1981; p 687. (b) Hummelen, J. C.; Meijer, E. W.; Wynberg, H. *Chem. Abstr.* **1984**, *100*, 209242h (PTC Int. Appl. WO 83 03,604).

(31) (a) Schaap, A. P.; Kaklika, K. A. *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic: New York, 1979; Chapter 6. (b) Kellog, R. M.; Kaiser, J. K. *J. Org. Chem.* **1975**, *40*, 2575.

(32) Adam, W.; Encarnacion, L. A. A. *Chem. Ber.* **1982**, *113*, 2636.

(33) Kopecky, K. R.; Filby, J. F.; Mumford, C.; Lockwood, P. A.; Ding, J.-Y. *Can. J. Chem.* **1975**, *53*, 1103.

(34) (a) Nelsen, S. F.; Teasley, M. F. *J. Org. Chem.* **1986**, *51*, 3221. (b) Kapp, D. L.; Teasley, M. F.; Perner, R. J., unpublished work. (c) Teasley, M. F., unpublished work.

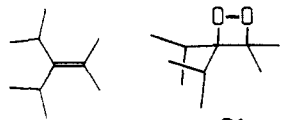


16 17 18 19

which divert the intermediates from the CRCC pathway is responsible for this effect, which is most useful synthetically and was not observed for preparations of the stabler **2** or **15**.

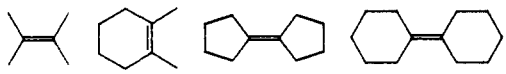
Dioxetane **17** proved to be rather unstable, both to heat and acid, but conditions were worked out (20:1:1 CH_2Cl_2/TFA/TFAA, −78 °C, 2% 5^+ as catalyst, followed immediately by a basic quench) which allow its isolation in 67% yield, although standing at room temperature in $CDCl_3$ causes conversion of **17** to cleaved aldol condensation product **18**, presumably catalyzed by acidic impurities in the NMR solvent. Even extraction of **17** solutions with 10% HCl led to its destruction, although in this case diketone **19** was isolated. It seems paradoxical that an acidic solvent greatly improves the reaction to make an especially acid sensitive product, but the reaction mixture was rapidly base quenched, and **17** is stable to the acidic solvent for short periods of time at −78 °C. We think it is noteworthy that homoadamantylene–adamantylede rearrangement was not observed during CRCC oxygenation of **16**. No **14** was detected.

1,1-Diisopropyl-2,2-dimethylethylene (**20**) has been



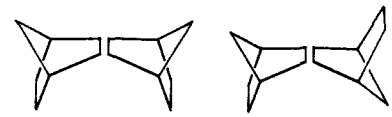
20 21

successfully converted to its dioxetane, **21**, in about 30% yield under CRCC conditions, showing that even acyclic compounds can be employed,[34b] but very different behavior was shown by olefins which lack α-branched carbons, such as **22–25**. They do not show ECbE cyclic



22 23 24 25

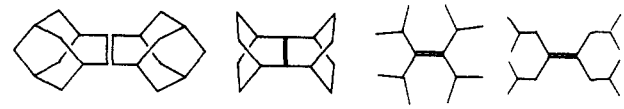
voltammograms under O_2, indicating that dioxetane cation radicals are not produced upon reaction of their radical cations with oxygen. In chemical oxidations, on the order of 50 mol % of 5^+ was required for olefin consumption, and dioxetanes are not major products, if any at all are formed.[34b] The principal products from **22** are acetone, pinacolone, and the formal adduct of hydrogen peroxide across the double bond, but quantitative study of these reactions, which differ substantially from the reactions described above, has not been carried out. Interestingly, sesquinorbornenes **26**[35] and **27**,[36] despite their α-branching and Bredt's rule protection, also do not show ECbE electrochemistry, although $\mathbf{26}^{\bullet+}$ and $\mathbf{27}^{\bullet+}$ are rapidly destroyed by O_2. Like



26 27

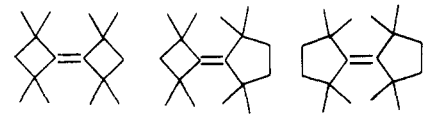
22–25, the sesquinorbornenes require large amounts of chemical oxidant for complete olefin consumption, so a long-chain oxygenation reaction is not occurring. Their products are complex. No dioxetanes have been detected, and chlorine-containing oxygenated products are formed when $\mathbf{5}^{\bullet+}SbCl_6^-$ is used as oxidant, while no oxygenated products were observed with $NO^+PF_6^-$.[34c] Our working hypothesis is that addition reactions to the less hindered unbranched and more reactive sesquinorbornene compounds are too rapid to allow efficient CRCC dioxetane formation and that the open addition product of olefin with oxygen is trapped by a second molecule of olefin or loses O_2 faster than it closes.

At the other end of the olefin addition reactivity scale, no effect of oxygen was observed on the cyclic voltammetry curves for sesqui-substituted bis-bicyclic compounds (**28**[37] and **29**[38]) or for tetra-α-branched (**30**),[39]



28 29 30 31

tetra-β-branched (**31**),[34b] or tetra-tertiary compounds (**32–34**).[40] All are presumably too hindered for oxygen to add rapidly enough relative to O_2 loss closure and electron transfer to compete and allow oxygenation to occur.



32 33 34

CRCC Oxygenation of Dienes

Barton and co-workers[5] showed that a variety of Lewis acids catalyze endoperoxide formation from dienes and triplet oxygen, both in the dark and with photostimulation. A particularly useful catalyst for the dark reaction was shown to be $\mathbf{4}^{\bullet+}$ and for the light-catalyzed reactions, triphenylmethyl cation. Barton suggested mechanisms in which the function of the Lewis acid is to catalyze intersystem crossing to overcome the multiplicity problem in adding triplet oxygen to singlet diene to give singlet endoperoxide. These reactions were suggested to involve cation radical intermediates by Bartlett,[4] Haynes,[41] and Tang and coworkers[42] in 1978, but the short lifetimes of the diene cation radicals chosen for study made the experimental

(35) (a) Paquette, L. A.; Carr, R. V. C.; Boehm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1980**, *102*, 1186. (b) Paquette, L. A.; Ohkata, K.; Carr, R. V. C. *Ibid.* **1980**, *102*, 3303. (c) Paquette, L. A.; Carr, R. V. C. *Ibid.* **1980**, *102*, 7553. (d) Paquette, L. A.; Schaefer, A. G.; Blount, J. F. *Ibid.* **1983**, *105*, 3642.

(36) (a) Barlett, P. D.; Blakeney, A. J.; Kimura, M.; Watson, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 1383. (b) Watson, W. H.; Galloy, J.; Bartlett, P. D.; Roof, A. A. M. *Ibid.* **1981**, *103*, 2022.

(37) (a) Gill, G. B.; Hands, D. *Tetrahedron Lett.* **1971**, 181. (b) Bolema, E.; Wynberg, H.; Strating, J. *Ibid.* **1971**, 4029.

(38) Nelsen, S. F.; Kapp, D. L. *J. Org. Chem.* **1984**, *50*, 1339.

(39) (a) Langler, R. F.; Tidwell, T. T. *Tetrahedron Lett.* **1975**, 777. (b) Bomse, D. S.; Morton, J. H. *Ibid.* **1975**, 781.

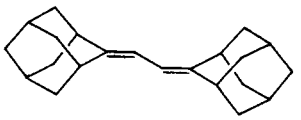
(40) Gerson, F.; Lopez, J.; Krebs, A.; Roger, W. *Angew. Chem.* **1981**, *93*, 106; *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 95.

(41) (a) Haynes, R. K. *Aust. J. Chem.* **1978**, *31*, 121, 131. (b) Haynes, R. K.; Probert, M. K.; Wilmot, I. D. *Ibid.* **1978**, *31*, 1737.

(42) Tang, T.; Yue, H. J.; Wolf, J. F.; Mares, F. *J. Am. Chem. Soc.* **1978**, *100*, 5248.

evidence for this suggestion rather ambiguous.

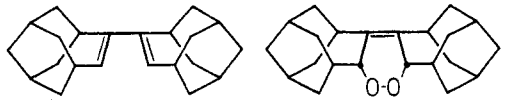
We took the approach of studying highly substituted, Bredt's rule protected dienes which would give cation radicals with long enough lifetimes to allow electrochemistry to help establish the reaction mechanism. Biadamantylideneethylene, **35**, gave identical cyclic



35

voltammograms in the absence and presence of oxygen, showing that $35^{\bullet+}$ does not react rapidly with oxygen.[43] Although the large alkyl groups prevent attaining an s-cis conformation, so that endoperoxide formation is sterically prohibited, we were initially surprised that one of the double bonds was not converted to a dioxetane, because $35^{\bullet+}$ is far less hindered than $1^{\bullet+}$, and we had expected that oxygen addition would be much faster. This might be true, but addition of oxygen to $1^{\bullet+}$ is reversible, and the adduct from $35^{\bullet+}$ would have allylic stabilization; even if addition occurs, oxygen loss apparently is faster than closure of the open β-peroxy carbocation.

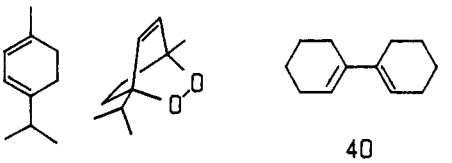
Bihomoadamantene (**36**) was chosen as a protected diene which ought to have an s-cis conformation available, and its neutral form appeared by UV spectroscopy to be a mixture of an untwisted, presumably s-trans form and a substantially twisted, presumably s-cis form from the observed λ(max) values of 244 and 202 nm. $36^{\bullet+}$ showed a broad visible absorption maximum at 745 nm, considerably red-shifted from untwisted models like $35^{\bullet+}$, and hence apparently substantially twisted, suggesting that it might be in the s-cis conformation. The cyclic voltammogram of **36** indi-



36 37

cated that ECbE behavior with a very fast oxygen addition was occurring, and oxidation with $5^{\bullet+}$ produced endoperoxide **37** in 84% isolated yield, in the 20:1:1 solvent mixture.[43] As previously observed with **16**, the chain length for **36** consumption substantially increased when the acidic solvent mixture was employed, from **22** to **53**. Obtaining **37** in good yield under CRCC conditions is especially significant because diene **36** does not give significant amounts of **37** upon treatment with $^1O_2$; at least six products were obtained, and most appeared to have one double bond intact. We suggest that production of **37** in the CRCC reaction is a result of the separate CO bond forming steps. The cation radical with one CO bond formed (a vinologue of $A^{\bullet+}$, Scheme I) has allyl cation resonance which lines up the p orbitals which must become parallel in **37** but are substantially twisted in **36**.

The unprotected diene α-terpinene (**38**) shows very poor electrochemical behavior, but its rather chemically irreversible oxidation wave completely disappeared under an oxygen atmosphere, which is consistent with ECbE electrochemistry and a very large k_2 value. A



38 39 40

completely irreversible oxidation wave indistinguishable from that of the endoperoxide ascaridole (**39**) appeared at higher potential under an oxygen atmosphere. The chain length for **38** consumption was about 260 at −78 °C in a 200:1:1 solvent mixture, and **39** was isolated in 96% yield after one crystallization.[43] Although $39^{\bullet+}$ does not survive the several milliseconds required for observation of chemical reversibility in a cyclic voltammogram even at −78 °C, its lifetime is apparently enough to obtain an efficient CRCC oxygenation reaction.

In direct contrast to this extremely favorable CRCC oxygenation, we completely failed to achieve any oxygenation of 1,3-cyclohexadiene, only isolating a mixture of the Diels–Alder dimers. Bauld and co-workers[44] have emphasized the utility of CRCC conditions for Diels–Alder adduct formation, and we think it is clear that the alkyl group substitution of **38** is responsible for slowing down Diels–Alder adduct formation enough to allow oxygenation to proceed in this case. In our hands, formation of the endoperoxide from bicyclohexenyl (**40**) under CRCC conditions was not very clean, and we never got the yield over 39%, far from the 74% achieved by Barton and co-workers[5] using $4^{\bullet+}$ as initiator. It is not yet clear whether the CRCC mechanism is occurring for oxygenation of less substituted dienes, where short cation radical lifetimes make it difficult to demonstrate that the cation radical is oxygenating, and their higher $E^{\circ\prime}$ values should make cation radical formation slower, but this mechanism clearly is operative for more substituted dienes.

Conclusion

This work has demonstrated that cation radicals carry the kinetic chain in the formation of peroxides from certain unsaturated hydrocarbons and dioxygen. A principal mechanistic contribution has been the formulation of the CO bonds as being formed in separate steps, so that there are two cation radical intermediates (Scheme I for the monoolefin to dioxetane case). Although the β-peroxy carbocation intermediate $A^{\bullet+}$ has not been spectroscopically detected, its presence has been inferred from trapping reactions and a stereochemical result. These reactions allow the preparation of compounds which are not available by other reactions; we do not believe that **15**, **17**, or **37** could be prepared by other published methods than CRCC reaction. The low temperatures at which CRCC reactions can be run, short reaction times, and simple workup make these reactions attractive for preparative work. Despite the general similarity in products from singlet dioxygen and CRCC triplet dioxygen addition reactions, the great difference in mechanism causes significant differences in which hydrocarbons will give dioxetanes

(43) Nelsen, S. F.; Teasley, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 5503.

(44) (a) Bellville, D. J.; Wirth, D. W.; Bauld, N. L. *J. Am. Chem. Soc.* **1981**, *103*, 718. (b) Bellville, D. J.; Bauld, N. L. *Ibid.* **1982**, *104*, 2665. (c) Bellville, D. J.; Bauld, N. L.; Pabon, R.; Gardner, S. A. *Ibid.* **1983**, *105*, 3584. (d) Pabon, R. A.; Bellville, D. J.; Bauld, N. L. *Ibid.* **1983**, *105*, 5158. (e) Pabon, R. A.; Bellville, D. J.; Bauld, N. L. *Ibid.* **1984**, *106*, 2730.

and endoperoxides by the two reactions; one or the other method is definitely preferred for many cases.

On the other hand, the range of hydrocarbon structural types for which CRCC oxygenations have been shown to occur is extremely narrow. Reaction to give dioxetanes from tetraalkylolefins has not been detected unless 1,1-bis-α-branched alkyl substituents are present, yet too much steric hindrance also prevents oxygenation. The diene to endoperoxide reaction requires some steric hindrance for oxygenation to compete effectively with CRCC Diels–Alder reaction but is more tolerant of steric hindrance than is singlet dioxygen addition, as shown by the successful formation of **37**. Considerably more work defining what hydrocarbon structural types are necessary to observe CRCC reactions is clearly necessary. Thermodynamic constraints appear to seriously limit the reactions which are plausible. Because peroxide cation radicals oxidize near 2.3 V vs. SCE, chain oxygenations of hydrocarbons to peroxides will not work for most mono- or dialkylolefins. O_2 and starting diene (as in the CRCC Diels–Alder reaction[44]) are not the only components possible for reaction with a cation radical, but the necessity for the product being harder to oxidize than the starting hydrocarbon severely limits the compounds which can be added in chain fashion.

σ–π interactions are unusually large in cation radicals, which was argued to lead to the unusually large olefin face selectivities observed in dioxetane formation from **9** and *syn*-**6**. Such large effects caused by fairly long range electronic interactions are both interesting theoretically and would be of practical importance if they can be predicted and controlled. We believe that a great deal of interesting chemistry remains to be discovered for cation radicals.

It is a pleasure to thank my particularly able co-workers who studied the CRCC oxygenation reaction in Madison, Dr. R. Akaba, D. L. Kapp, and M. F. Teasley. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Wisconsin Alumni Research Foundation, and the National Science Foundation for partial financial support of this work, as well as the Amoco Oil Company for fellowship support for D.L.K. and M.F.T. during parts of this work.

DNA Flexing, Folding, and Function

HENRYK EISENBERG

Polymer Department, The Weizmann Institute of Science, Rehovot 76100, Israel

Received January 5, 1987 (Revised Manuscript Received May 8, 1987)

Huge Size Genome DNA

To a biased chemist DNA certainly is the most interesting macromolecule created by either nature or man. Not until the beginning of the second half of the twentieth century was the functional role of DNA as carrier of biological inheritance clearly established. In 1953 Watson and Crick,[1] in proposing the guanine-cytosine (G-C), adenine-thymine (A-T) base paired structure for double-helical DNA, note that "it has not escaped our notice that the specific base pairing postulated immediately suggests a possible copying mechanism for the genetic material." One page in *Nature (London)*, stating the basic model and its far-reaching biological implications, set the course of the life sciences for decades to follow. DNA can be likened to a linear computer tape in which important information transmitted by heredity is encoded as sets of consecutive bases (A, C, G, T) inscribed in long sequences; the well-known "genetic code" is composed of base triplets, each coding for a given amino acid. Base triplets also exist for signaling the start or the termination of a given message.[2] DNA replication[3] ensures the transmittance of the genetic message to subsequent generations, whereas transcription to messenger RNA (mRNA) eventually leads to translation into a large number of proteins. Proteins in turn constitute the "chemical" machinery of the organism, some of them strongly interacting with DNA in regulating its structure and function, in particular the replication and transcription processes.

DNA as a macromolecule is basically different from the globular proteins with which it is intimately connected in the circle of life sketched above. Globular proteins are moderate in size (extending over distances of about 3–10 nm) and are composed of one or more polypeptide chains (around 10–100 kg/mol (kDa) molar mass). Following synthesis on the ribosome they fold into globular structures and stay this way throughout their life cycle, maintaining active and regulatory binding sites. DNA, on the other hand, is not active in a folded form, though it must maintain essentially folded structures, as will presently become apparent. In contrast to the proteins DNA is of much larger size.[3] Thus, for instance, the DNA of a lower order organism, the *E. coli* bacterium, codes for about 4000 proteins and contains about 4×10^6 base pairs (bp) in the Watson–Crick double-helical structure. The molar mass of one bp is, on the average, 662 g/mol. Stretched out linearly, this DNA would have a molecular length of 1.36 mm, while the diameter of the molecule is only about 2.5 nm.

Henryk Eisenberg was born in 1921 and educated at the Hebrew University in Jerusalem. He has been at the Polymer Department of the Weizmann Institute since 1949. In 1973 he was a Fogarty Scholar in Residence at the National Institutes of Health, Bethesda, MD. Research interests include nucleic acid and chromatin structure, structure of proteins, and protein–nucleic acid interactions in extreme halophilic bacteria, polyelectrolytes, thermodynamics of multicomponent systems, ultracentrifugation, scattering of light, X-rays, and neutrons.

(1) Watson, J. D.; Crick, F. H. C. *Nature (London)* **1953**, *171*, 737.
(2) Stryer, L. *Biochemistry*, 2nd ed.; Freeman: San Francisco, 1981.
(3) Kornberg, A. *DNA Replication*; Freeman: San Francisco, 1980.

0001-4842/87/0120-0276$01.50/0 © 1987 American Chemical Society