The Unusual Reactions of Singlet Oxygen with Isomeric 1,4-Di-*tert*-butoxy-1,3-butadienes. A $2_s + 2_a$ Cycloaddition

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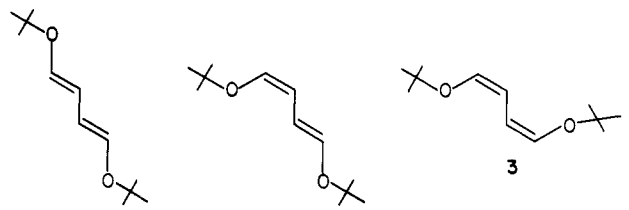
Abstract: The reactions of singlet oxygen with (1*E*,4*E*)-, (1*E*,4*Z*)-, and (1*Z*,4*Z*)-1,4-di-*tert*-butoxy-1,3-butadiene are reported. The reactions with all three dienes lead to predominately dioxetane products. Spectral evidence is presented for the configurations of these dioxetanes, and two mechanisms are suggested for their formation. The first mechanism is a concerted $2_a + 2_s$ cycloaddition and the second a reaction which proceeds through a zwitterionic intermediate. Solvent effect data and kinetic data are presented in support of these suggestions.

The reactions of singlet oxygen with conjugated butadienes are important reactions for the 1,4-functionalizations[1] of these versatile compounds, yet the compatibility of substituents on[2] and the mechanisms[3] of these reactions have not received extensive scrutiny. Only recently have the complexities[4] of these reactions been appreciated.

The additions of singlet oxygen to substituted 1,3-butadienes can lead to ene,[5] 2 + 2,[6] or 4 + 2 products.[7] In general when sterically permitted, 4 + 2 cycloadditions appear to be the preferred mode of reactivity. A detailed study of those systems, however, in which the ene, 2 + 2, and 4 + 2 reactions compete, can provide insight into the mechanisms of these reactions.

We report here the results of a study of the reactions of singlet oxygen with isomeric *EE*-**1**, *EZ*-**2**, and *ZZ*-**3** 1,4-di-*tert*-butoxy-1,3-butadienes in which 4 + 2 cycloadditions are not the preferred pathways even for the *EE* diene **1**. These reactions provide important mechanistic information on dioxetane formation and underscore the inadequacies of the current mechanistic picture of endoperoxide formation.



1 **2** **3**

Results

The additions of singlet oxygen to dienes **1**, **2**, and **3** were accomplished by irradiation of oxygen-saturated acetone-d_6 solutions of each diene at −78 °C in the presence of the sensitizer Rose Bengal. The complete disappearance of these dienes occurred in approximately 25 min. Control experiments in a nitrogen atmosphere utilizing otherwise identical reaction conditions demonstrated that less than 5% isomerization of **1**, **2**, or **3** could occur in this time period. Dioxetanes were the major products of these reactions in each case and an endoperoxide was formed only in the singlet oxygenation of diene **2** (Figure 1). The ratios of these products in each case were independent of the extent of reaction. The endoperoxide was isolated by flash column chromatography, but the sensitivity of the dioxetanes precluded their separation and purification. The dioxetane structures, however, are totally consistent with their spectral properties (vide infra).

Table I. NMR Data for the Oxidation Products

	4	5	6	7	8
^{1}H NMR[a]					
δ H_1 (ppm)	6.41	6.33	6.38	5.38	6.35
δ H_2	5.49	5.90	5.99	5.89	6.41
δ H_3	5.20	5.32	4.82		4.97
δ H_4	7.16	7.06	6.85		6.80
δ CH_3	1.23	1.22	1.24	1.12	1.22
	1.11	1.19	1.12		1.12
J_{12} (Hz)	6.2	5.5	6.2	1.5	5.1
J_{23}	10.3	10.6	10.6		10.6
J_{34}	11.7	12.1	6.2		6.2
^{13}C NMR					
δ C_1 (ppm)	100.94[b]	99.6[b]	100.94	89.33	99.14[b]
δ C_2	86.75	83.13	80.41	125.07	*c*
δ C_3	99.28[b]	98.3[b]	97.59		96.40[b]
δ C_4	150.27	149.54	147.04		146.25
δ CH_3	26.59	26.81	26.57		26.78
	26.10	26.10	26.05	27.00	*c*
δ C_q	76.93	76.69	77.01		76.63
	75.27	74.78	75.33	73.86	74.76

[a] All NMR were taken at −80 °C in acetone-d_6 immediately after photolysis. [b] Assignments may be switched. [c] Not observed buried under another peak.

The formations of all these products were inhibited in the presence of the quencher DABCO (1,4-diazobicyclo[2.2.2]octane), illustrating their singlet oxygen origin.

Product Identification. The proton NMR spectra from 4.7 to 7.2 ppm for the reactions of all three dienes with singlet oxygen are shown in Figure 2. These data along with the ^{13}C NMR data are also tabulated in Table I. The four-spin network for each of the dioxetanes was conveniently established by single frequency decoupling. The four doublets d, h, l, and p belong to different spin networks and represent proton H_4 on each of the dioxetanes. The magnitude of the H_4–H_3 coupling constants allows differentiation of the dioxetanes with a cis double bond (**6** and **8**) from the two dioxetanes with a trans double bond (**4** and **5**). The ring substituent stereochemistry was established in each case by the examination of the H_1–H_2 coupling constant. Extensive studies have documented that cis vicinal coupling constants are larger than trans in both oxetanes[8] and dioxetanes[9] by 0.5 to 1.5 Hz. The chemical shifts are also consistent with the well-documented steric effect[10] providing additional evidence for the accuracy of these assignments. In particular (1) δ H_4 and H_3 in the trans olefinic linkages are downfield of δ H_4 and H_3, respectively, in the cis olefinic linkages, (2) δ H_2 in the trans-ring substituted dioxetanes are downfield of δ H_2 in their cis-ring substituted

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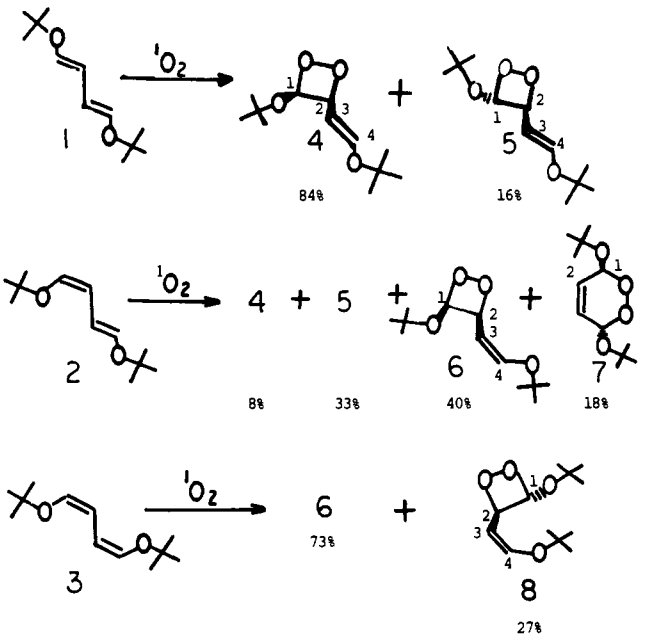


Figure 1. Reaction products from the singlet oxidation of dienes **1**, **2**, and **3**.

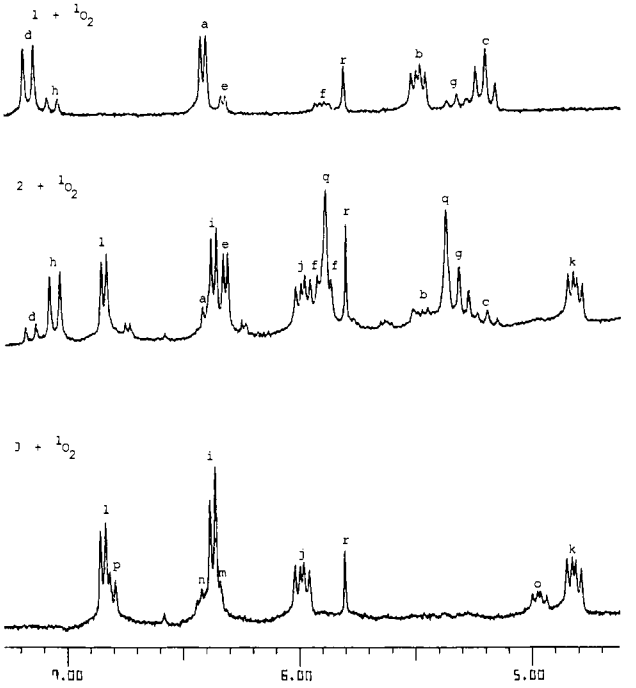
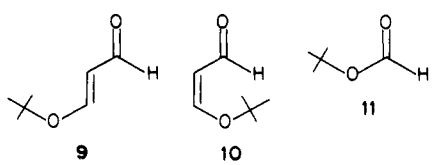


Figure 2. The proton NMR spectra from 4.7 to 7.2 ppm for the reactions of **1**, **2**, and **3** with singlet oxygen: (a) 4-(H_1); (b) 4-(H_2); (c) 4-(H_3); (d) 4-(H_4); (e) **5**-(H_1); (f) **5**-(H_2); (g) **5**-(H_3); (h) **5**-(H_4); (i) **6**-(H_1); (j) **6**-(H_2); (k) **6**-(H_3); (l) **6**-(H_4); (m) **8**-(H_1); (n) **8**-(H_2); (o) **8**-(H_3); (p) **8**-(H_4); (q) endoperoxide (**7**); (r) impurity.

isomers, and (3) δ H_2 in the cis olefinic linkages are downfield of δ H_2 in the trans olefinic isomers.

The dioxetanes were indefinitely stable at −78 °C but decomposed slowly at room temperature to produce as the only products the α,β-unsaturated aldehydes **9** and **10** and *tert*-butylformate **11**. The spectral data (See Experimental Section) are consistent



9 **10** **11**

with the assignments of these decomposition products. The cis acrolein **10** slowly isomerized to **9** at room temperature or upon attempted chromatographic separation, and its spectral data were obtained from the NMR spectra of the reaction mixtures.

The possibility that singlet oxygen-induced isomerizations[4] of these dienes are responsible for the nonstereospecificities of these reactions is unlikely. Examination of the reaction mixtures after partial photooxidation did not reveal the presence of any isomeric diene. In addition, the formation of dioxetane **4** in the reaction of diene **1** by isomerization and addition of singlet oxygen to the resultant *EZ* diene **2** cannot have occurred since the other products from the reaction of **2** were not detected.

Solvent Effects. The reactions of singlet oxygen with dienes **1**, **2**, and **3** were investigated in CD_2Cl_2/acetone-d_6 mixtures. The chemical shifts of H_1 and H_4 in the dioxetanes changed as much as 0.4 ppm while the chemical shifts of H_2 and H_3 were invariant as a function of solvent. The sensitivities of these chemical shifts to the mole fraction of acetone were remarkably similar for all the dioxetanes. These data are reported in Table II.

The assignments of the chemical shifts to the dioxetanes were immensely simplified despite the dramatic changes in the appearance of the spectra since the chemical shifts were linearly related to the mole fraction of acetone-d_6. The chemical shift of the protons α to the alkoxy groups in endoperoxide **7** is also linearly related to the mole fraction of acetone-d_6. The α-proton chemical shift in the endoperoxide, however, was observed to be less sensitive to solvent change than the α-protons in the dioxetanes. The slope and the correlation coefficients for the plots of these chemical shifts vs. the mole fraction of acetone are also reported in Table II.[11]

The percentages of the products formed in these reactions are reported in Table III. These values were determined by inte-

Table II. The Proton NMR Data for Dioxetanes **5**, **6**, and **8** and Endoperoxide **7** as a Function of Solvent Composition

		chemical shift[a] mol fraction of acetone					
compd	proton	1	0.778	0.466	0.178	slope	*r*
8	H_1	6.35	6.29	6.20	6.08	0.325	0.9947
	H_2	6.41	6.43	6.45	6.41		
	H_3	4.97	4.98	4.98	4.94		
	H_4	6.80	6.73	6.60	6.46	0.416	0.9966
5	H_1	6.33	6.26	6.17	6.11	0.269	0.9962
	H_2	5.90	5.89	5.86	5.86		
	H_3	5.32	5.33	5.33			
	H_4	7.06	6.98	6.82	6.66	0.492	0.9968
6	H_1	6.38	6.32	6.20		0.34	0.9957
	H_2	5.99	6.00	6.01	5.96		
	H_3	4.82	4.80	4.78	4.72		
	H_4	6.85	6.77	6.63		0.414	0.9982
7	H_1	5.38	5.37	5.33	5.27	0.135	0.9712
	H_2	5.89	5.88	5.86	5.85		

[a] All chemical shifts are reported relative to Me_4Si.

Table III. Product Percentages in the Reaction of Singlet Oxygen with **1**, **2**, and **3** as a Function of Solvent Compositions

		%				
diene	mol fraction of acetone-d_6	**4**	**5**	**6**	**7**	**8**
1	1	84	16			
	0.778	88	12			
	0	91	9			
2	1	8	33	40	18	
	0.778	6	30	39	25	
	0.466	2	31	42	20	4
	0.178	5	22	39	27	6
3	1			73		27
	0.778			71		29
	0.466			39.1		60.9
	0.178			12.4		87.6
	0			10.9		90.1

(11) The coupling constants remained the same in all solvents studied.

Table IV. Young Second-Order Rate Constants for the Reactions of Singlet Oxygen with Dienes 1, 2, and 3

compd	solvent	k (M^{-1} s^{-1}) × 10^{-7}
1	acetone	9.1
	CH_2Cl_2	8.5
2	acetone	5.7
	CH_2Cl_2	5.3
3	acetone	1.5
	CH_2Cl_2	2.0

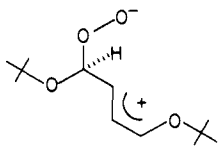
gration of the ^1H NMR's of the reaction mixtures at −78 °C and are only accurate to ±5%.

Kinetic Studies. The rates of singlet oxygen addition to dienes **1**, **2**, and **3** were measured in both methylene chloride and acetone, utilizing the Young method.[12] The results of these studies are reported in Table IV. The rates reported are the average of three to five independent determinations. Acceptable rates for the reactions of all three dienes were obtained by keeping their concentrations and conversions low. At higher concentrations, the dienes quenched the fluorescence of the 1,3-diphenylisobenzofuran probe. Similar quenching of the fluorescent probe was observed in studies by Foote[13] and Mehrsheikh-Mohammadi.[14] Details of the kinetic studies are reported in the Experimental Section.

Discussion

***ZZ* Diene 3.** The formation of isomeric dioxetanes from this diene which maintains its stereochemical integrity can most easily be explained by invoking a freely rotating intermediate. Of the previously considered mechanisms,[15-18] only those which invoke zwitterionic[19] or biradical[20] intermediates are consistent with these data.

The predominate formation of a cis-substituted dioxetane in the acetone-d_6 reaction also demands that the freely rotating intermediate have substantial ionic character. This phenomenon is a homoallylic example of the "inside alkoxy" effect. Houk[21] has recently pointed out that the propensity for alkoxy groups to adopt the most hindered environment in cycloadditions (the "inside alkoxy" effect) has an electronic origin and should be manifested to the greatest extent in electrophilic reactions. In addition, the absence of any dioxetane formed in the reaction in which the nonoxidized double bond has isomerized is consistent with the anticipated difficult rotation[22] about the allylic cation moiety in the zwitterionic intermediate **12**.



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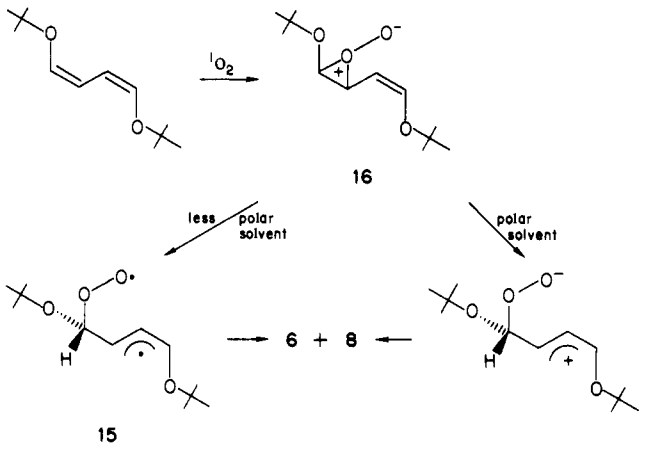
Schaap and Tontapanish[9] have also observed an electronic preference for the formation of cis-substituted dioxetanes in the reaction of enol ethers with singlet oxygen suggesting that ionic

Scheme I



intermediates are not only important in the reaction of diene but olefinic substrates as well.

The solvent effect data in Table III support this mechanistic suggestion. As the solvent becomes richer in the less polar solvent, methylene chloride, the yield of the trans-ring substituted dioxetane **8** increases. This is exactly the result expected as the character of the freely rotating intermediate becomes more radical-like in the less polar solvent. Steric effects rather than electronic effects dictate the stability of the diradical intermediate.

Support for this continuum theory for biradicals and zwitterions is provided by Hoffman[23] and Salem,[24] who have examined tetramethylene diradical **13** and zwitterion **14** from a theoretical perspective. They have concluded that the description of the

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tetramethylene species as **13** or **14** is dictated by substituents. Foote[19b] has suggested that solvent effects can also determine the character of these intermediates.

Despite the dramatic solvent effect on product composition only a minor solvent effect on the rate of reaction of diene **3** is observed (Table IV). This suggests that the entropy controlled[25] initial interaction of singlet oxygen with **3** and the product determining step are not the same. A mechanism consistent with all these data is presented in Scheme I. Our results do not allow us to determine if perepoxide **16** is an intermediate or transition state. Our results with the *EE* diene **1** (vide infra), however, suggest that the initial interaction with singlet oxygen must have perepoxide symmetry.

***EE* Diene 1.** This diene also reacts with singlet oxygen to form two different dioxetanes **4** and **5** (Figure 1). The insensitivity of the product composition as a function of solvent (Table III), however, suggests that this reaction is very different than the reaction of *ZZ* diene **3**. We suggest that perepoxide intermediates and/or transition states **17** and **18** (Chart I) are energetically unobtainable and that instead $2_s + 2_a$ transition states (**19** and **20**) are traversed. The perepoxide **16** is stabilized by virtue of interactions of the pendant oxygen with both the *tert*-butoxy[26] and vinyl groups.[27] Only one such interaction is available in **17** and **18**. The "cis effect"[28] and the directive effect of the methoxy

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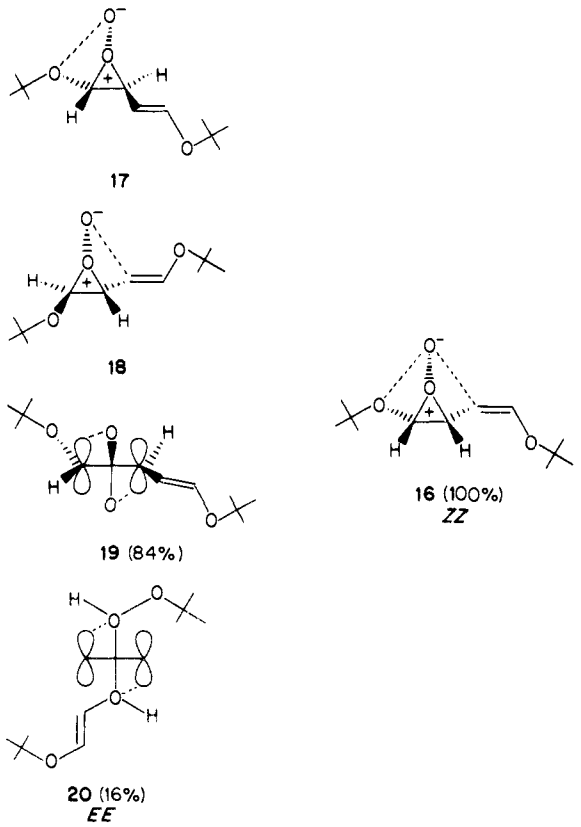
Chart I



group[29] have been suggested to be manifestations of this attractive interaction in the ene reaction. Ab initio calculations with a STO-3G basis set and the unrestricted MINDO/3 (UM3) technique both agree that in the absence of such interactions the perepoxide is not a viable intermediate on the ene energy surface.[30]

The much reduced solvent effect in ketene cycloadditions,[31] a well-documented $2_s + 2_a$ cycloaddition, in comparison to 2 + 2 cycloadditions which proceed via zwitterions,[32] has also been demonstrated.[33] These ketene cycloadditions occur more rapidly with cis than trans olefins, reflecting steric demands in the transition states. The minimal steric requirements of singlet oxygen clearly do not preclude attainment of the $2_s + 2_a$ transition state even in the addition to trans double bonds.

***EZ* Diene 2.** The reaction of singlet oxygen with **2** produces three dioxetanes in acetone-d_6 and all four dioxetanes in CD_2Cl_2 rich solvent mixtures (Figure 1). The very different ratio's of **4** and **5** formed in the acetone-d_6 reactions of singlet oxygen with the trans double bond in **1** (**4**/**5** = 5.25) and the cis double bond in **2** (**4**/**5** = 0.242) are consistent with our suggestion of two different mechanisms for their formations.

Diene **2** also reacts to form the endoperoxide **7**. The formation of an endoperoxide in this reaction but not in the reaction of **1** is unexpected in view of the anticipated *s-cis* population in these two dienes and totally without precedent. The rearrangement of the endoperoxide formed in the reaction of **1** to a dioxetane does not provide a satisfactory explaination for this observation since this rearrangement would have to be rapid even at −78 °C to go undetected. The endoperoxide—dioxetane rearrangements which have been reported[34] occur at ambient or higher temperatures and often require acid catalysis. A discussion of this phenomenon and the possibility of conformationally dependent quenching of singlet oxygen and/or anomeric interactions will be presented in a subsequent manuscript.

Conclusion

We have suggested two different mechanistic pathways for the formation of dioxetanes: (1) a $2_s + 2_a$ cycloaddition in which the carbon–carbon double bond prefers to be the **2a** component, and (2) the collapse of a zwitterion/biradical intermediate which is formed from the opening of a perepoxide transition state or intermediate. The proposal of two different mechanisms rather than a single unified mechanism appears to be necessary. We cannot conceive of one single mechanism which can satisfactorily explain (1) the apparent suprafacial addition to the *ZZ* diene and antrafacial addition to the *EE* diene, (2) the observation of a solvent effect in the reaction of the *ZZ* diene and total absence of a similar solvent effect in the reaction of the *EE* diene, and (3) the different ratios **4**/**5** and **6**/**8** formed as a function of the configuration (**Z** or **E**) of the double bond involved in the reaction.

The $2_s + 2_a$ transition state is only accessible if the perepoxide is not stabilized by interaction of the pendant oxygen with cis substituents on the olefinic linkage. The $2_s + 2_a$ mechanism also differs from the zwitterionic mechanism by the insensitivity of the product ratio (**4**/**5**) to solvent polarity changes. A dramatic change in the product ratio (**6**/**8**) is observed when a zwitterion is on the reaction pathway. The absence of a substantial solvent effect on the rates of these reactions over the small polarity range examined does not mean that the sensitivity of these rates over a large solvent polarity range cannot be utilized as a universal test to distinguish between these two mechanisms. This point will be explored further.

Experimental Section

Preparative gas chromatographic separations were carried out on a Varian Aerograph 90-P utilizing a 0.25 in. by 20 ft column packed with 20% carbowax 20M on Chromosorb W. The retention times of the *ZZ*, *EZ*, and *EE* dienes were 89, 108, and 118 min, respectively, when the oven was set to 125 °C, the injector to 190 °C, the detector to 190 °C, and the collector to 170 °C. Proton and carbon NMR spectra were obtained on a JEOL FX270 at 270 and 67.83 MHz, respectively, and the chemical shifts referenced to Me_4Si. Mass spectral data were obtained on a VG-ZAB-1F by electron impact or ammonia chemical ionization. Kinetic studies were completed on a Perkin Elmer MPF-2A spectrofluorometer.

Acetone-d_6 (Aldrich) and bulk acetone were distilled from $CaSO_4$ under a N_2 atmosphere and stored over 4A molecular sieves. Methylene-d_2 chloride was filtered through activity 1 basic alumina prior to use. Bulk methylene chloride for preparative reactions was stirred over sulfuric acid, washed with water, dried over $MgSO_4$, and distilled from P_2O_5 prior to the basic alumina treatment.

(1*Z*,4*Z*)-1,4-Di-*tert*-butoxy-1,3-butadiene (3) was synthesized by the method of Hiranuma and Miller[35] and purified by preparative gas chromotography. ^1H NMR (acetone-d_6) δ 6.09 (dd, J = 3.2, 1.5 Hz, 2 H), 5.33 (dd, J = 3.2, 1.5 Hz, 2 H), 1.22 (s, 18 H). ^{13}C NMR (acetone-d_6) δ 138.04, 101.92, 76.20, 28.09.

(1*E*,4*Z*)-1,4-Di-*tert*-butoxy-1,3-butadiene (2) was synthesized by the method of Hiranuma and Miller[35] and purified by preparative gas chromatography. ^1H NMR (acetone-d_6) δ 6.54 (d, J = 12.4 Hz, 1 H), 6.02 (d, J = 6.6 Hz, 1 H), 5.79 (dd, J = 12.4, 11.0 Hz, 1 H), 4.94 (dd, J = 11.0, 6.6 Hz, 1 H), 1.21 (s, 9 H), 1.20 (s, 9 H). ^{13}C NMR (acetone-d_6) δ 142.39, 137.04, 104.93, 104.55, 76.28, 76.06, 28.12.

(1*E*,4*E*)-1,4-Di-*tert*-butoxy-1,3-butadiene (1) was synthesized by the method of Hiranuma and Miller[35] and purified by preparative gas chromatography. ^1H NMR (acetone-d_6) δ 6.39 (dd, J = 8.1, 2.9 Hz, 2 H), 5.45 (dd, J = 8.1, 2.9 Hz, 2 H), 1.18 (s, 18 H). ^{13}C NMR (acetone-d_6) δ 141.44, 107.59, 76.36, 28.42.

(3*E*)-3-*tert*-Butoxyacrolein (9) was isolated from the reaction mixtures by column chromatography. ^1H NMR (acetone-d_6) δ 1.42 (s), 5.49 (dd, J = 11.7, 8.8 Hz), 7.86 (d, J = 11.7 Hz), 9.36 (d, J = 8.8 Hz). ^{13}C NMR (acetone-d_6) δ 26.0 (q, J = 124 Hz), 80.52 (s), 110.94 (d, J = 160 Hz), 168.30 (d, J = 173 Hz), 190.37 (d, J = 167 Hz). Mass spectrum

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for $C_7H_{12}O_2$, found 128.0870 and calcd 128.0838.

(3*Z*)-3-*tert*-Butoxyacroleln (10). ^1H NMR (acetone-d_6) δ 1.41 (s), 5.02 (dd, J = 8.8, 6.6 Hz), 7.52 (d, J = 6.6 Hz), 10.0 (d, J = 8.8 Hz). ^{13}C NMR (acetone-d_6) 27.9 (q, J = 127 Hz), 80.96 (s[a]), 109.14 (d, J = 176 Hz), 159.7 (d, J = 172 Hz), 188.0 (d, J = 171 Hz) [a indicates the assignment may be switched with carbon in **11**].

***tert*-Butylformate (11).** ^1H NMR (acetone-d_6) δ 1.45 (s), 8.05 (s). ^{13}C NMR δ 161.28 (d, J = 221 Hz), 81.14 (s[a]) (a indicates the assignment may be switched with carbon in **10**).

3,6-Di-*tert*-Butoxy-4,5-dioxene (7) gave a positive ammonium thiocyanate-ferrous ammonium sulfate test. Ammonia chemical ionization mass spectrum: M^+ found 230.1562 and calcd 230.1519; MH^+ found 231.1424 and calcd 231.1597; MNH_4^+ found 248.1700 and calcd 248.1863. Proton and carbon NMR data are found in Table II.

Photolysis Conditions. An acetone-d_6 solution that was 0.013 M in (1*E*,4*E*)-1,4-di-*tert*-butoxy-1,3-butadiene (**1**) and 1×10^{-5} M in rose bengal was placed in a 5 mm NMR tube. This solution was saturated with oxygen for 25 min at -78 °C while being protected from the room light. This reaction mixture was then irradiated for 25 min at -78 °C with a Sylvania 750 Q/Cl tungsten-halogen lamp through a 0.5% $K_2Cr_2O_7$ filter solution. The reaction was monitored at -80 °C by low-temperature NMR.

Kinetic Studies. The Young method[12] was utilized to measure $k_r + k_q$ for the reactions of singlet oxygen with dienes **1**, **2**, and **3**. The dye (mesoporphyrin IX dimethyl ester) was irradiated with a Sylvania 750 Q/Cl tungsten-halogen lamp operated at 36-45 V. This irradiation source was placed at right angles to the excitation (418 nm) and emission (460 nm) light paths and focused through a Corning 3-68 filter (cutoff 540 nm). Six stock solutions containing different concentrations of the three dienes were utilized for each determination. The S_0/S_x value was kept below 7.6 for **1**, 5.3 for **2**, and 2.9 for **3** in order to avoid quenching the fluorescent probe diphenylisobenzofuran. Each kinetic determination resulted in a S_0/S_x plot with a correlation coefficient (r) greater than 0.999. The k_d utilized for acetone was 2.17×10^4 s^{-1} [36] and that for methylene chloride 1.0×10^4 s^{-1}.[37]

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Registry No. **1**, 86528-14-5; **2**, 86528-15-6; **3**, 79989-51-8; 4, 97336-93-1; **5**, 97372-91-3; **6**, 97372-92-4; **7**, 97336-94-2; **8**, 97372-93-5; **9**, 97336-95-3; **10**, 97336-96-4; **11**, 762-75-4.

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Kinetics and Mechanism of the Acid Hydrolysis of Mitomycins

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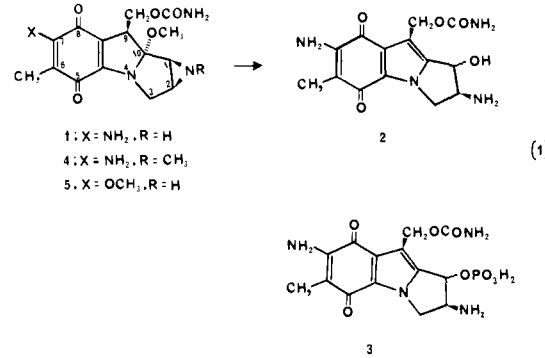
Abstract: First-order rate constants have been obtained as a function of pH and temperature for the hydrolysis of mitomycin C, mitomycin A, and porfiromycin to produce the corresponding 2-amino-1-hydroxymitosene. Rate constants are proportional to hydronium ion concentration at high pH (>4) and level at low pH when the aziridine ring of the mitomycin is protonated. Catalysis by added buffers is observed. A mechanism is proposed with the neutral mitomycin as the reactive species undergoing rate-limiting expulsion of methoxide in reactions catalyzed by hydronium ion and by added buffer acids. In a rapid step the cation so produced loses a proton to form an aziridinomitosene intermediate. This then undergoes rapid hydrolytic ring opening of the aziridine ring. This hydrolysis is triggered by the conjunction introduced in the methanol elimination.

Mitomycin C (**1**) is a potent antitumour antibiotic[1-3] which covalently binds[4] and cross-links[5,6] DNA. Since these effects are observed in the absence of cells only if a reducing agent is present,[7,8] the biologically active form of the drug is generally proposed to arise in the cell by reduction.[7,8] The term "bioreductive alkylating agent" has been introduced to designate agents of this type.[9] The possibility of using such drugs as agents specifically activated in hypoxic tumour cells has been discussed.[10]

Acidic conditions (pH 4) have been found to also activate the binding and cross-linking processes.[11] Mitomycin C under such conditions is converted into 2,7-diamino-1-hydroxymitosenes (**2**),[12-14] with the cis isomer predominating.[13,14] The alkylation of inorganic phosphate (structure **3**) and the phosphate group of various nucleotides can also be observed under these conditions.[15]



1: X = NH_2, R = H
4: X = NH_2, R = CH_3
5: X = OCH_3, R = H

2 (1)

3

Interestingly these same substances have recently been observed after reoxidation of the products of reductive metabolism of

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