Reaction of Singlet Oxygen with 4-Methyl-2,3-dihydro-γ-pyrans

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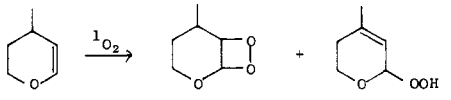
Abstract: 4-Methyl-1,3-dihydro-γ-pyran (**1**) reacts with singlet molecular oxygen to yield both a dioxetane **2** and an allylic hydroperoxide **3**, each of which is converted by heat into a single product stable under conditions of vapor chromatography. The product composition from **1** and from **1**-*4-d* has been determined in benzene and in acetonitrile, the ratio **2**/**3** being 26 times greater in the latter solvent. The tritium kinetic isotope effects at the α, β, and γ positions indicate that for both products in both solvents the transition state has a weakened H–C^{γ} bond, a strengthened H–C^{β} bond, and an H–C^{α} bond whose strength is not appreciably altered. Possible interpretations of these effects are discussed with respect to the detailed mechanism of attack of singlet oxygen on this enol ether, which is also compared with 4,4-dimethyl-1,3-dihydropyran (**4**).

It is generally agreed[2-6] that the [2 + 4] addition of singlet oxygen to 1,3-dienes to form endoperoxides is concerted and analogous to the Diels–Alder reaction [$2_s + 4_s$].[7] There is much ambiguity, however, regarding the mechanistic details of the [2 + 2] cycloaddition and ene reaction of singlet oxygen.

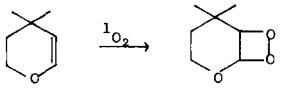
4-Methyl-2,3-dihydro-γ-pyran (**1**) has an activated double bond and an adjacent allyic hydrogen and is, therefore, capable of yielding upon reaction with singlet oxygen both 1,2 cy-



1 **2** **3**

cloaddition product, dioxetane **2,** and ene reaction product, allylic hydroperoxide **3.**

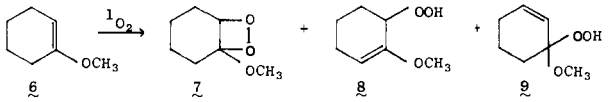
4,4-Dimethyl-2,3-dihydro-γ-pyran (**4**), on the other hand, lacks an allylic hydrogen and is hence prevented from under-



4 **5**

going an ene reaction; however, its double bond is still activated and should give dioxetane **5.**

1-Methoxycyclohexene (**6**), like dihydropyran **1,** has an activated double bond and adjacent allylic hydrogens; however,



6 **7** **8** **9**

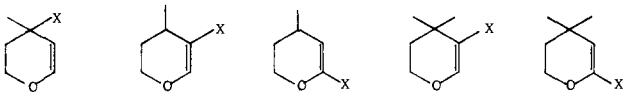
since the ether linkage is exocyclic, it has two points from which singlet oxygen might attack to give ene products **8** and **9.**

A thorough study and comparison of these three enol ether systems appeared to be a promising area in which significant clues to the mechanistic details of the ene and cycloaddition reactions might be found.

In this paper we describe the synthesis and photooxidation of dihydropyrans **1** and **4** and their isotopically labeled analogues, while in a later paper we shall present the results obtained from the study of the 1-methoxycyclohexene system.

In the simplest view, a concerted ene reaction to **1** should show a substantial primary kinetic isotope effect with respect to H at the allylic 4 position, while there should be none if the H abstraction is a sequel to the rate-determining step. In the limiting case of concerted, symmetrical addition to the double bond there should be small and equal secondary kinetic isotope effects at the two vinylic hydrogen atoms at C-5 and C-6. Departures from this simplest situation might be expected to show themselves in more subtle isotope effects.

Synthesis of Labeled Dihydropyrans. Compounds **1, 4, 10,**

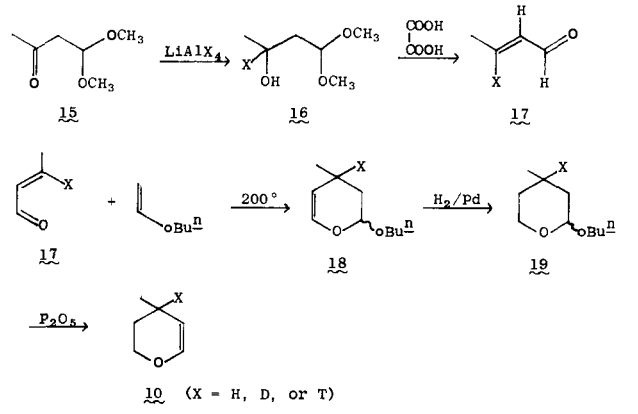


10 **11** **12** **13** **14**

11, 12, 13, and **14** (X = D or T) were synthesized.

Dihydropyran **1** was obtained from a [2 + 4] cycloaddition[8] of crotonaldehyde and vinyl *n*-butyl ether. The adduct **18** was reduced with hydrogen and treated with P_2O_5 to yield the desired product. The isotopically labeled crotonaldehyde needed for the synthesis of **10** (X = D or T) was prepared by reducing acetoacetaldehyde dimethyl acetal with isotopically labeled

Scheme I



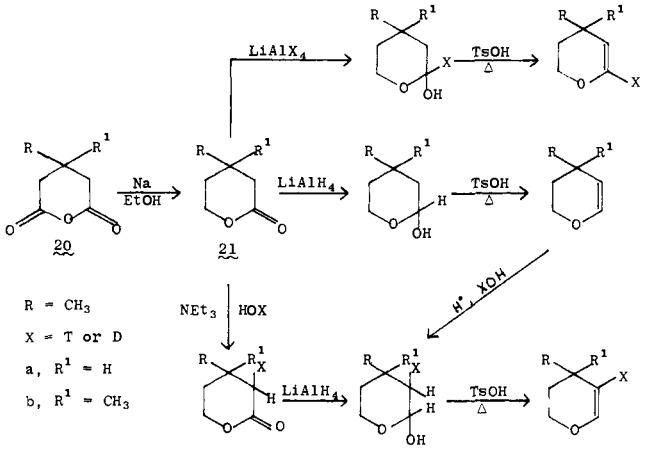
lithium aluminum hydride, and dehydrating the resulting alcohol with oxalic acid.[9] The sequence is shown in Scheme I.

4-Methyl-2,3-dihydro-γ-pyran-*6-t* (**12,** X = T) was synthesized as shown in Scheme II. Reduction of 3-methylglutaric anhydride (**20a**) with sodium in ethanol led to 3-methyl-δ-valerolactone (**21a**).[10] Inverse addition of isotopically labeled lithium aluminum hydride[11] to lactone **21** followed by acid dehydration of the resulting alcohol gave the desired product.

Dihydropyran **11** (X = T) can be prepared either[12] from **1** through an addition–elimination sequence with isotopically labeled water or via a base exchange of the α protons in lactone **21a** (followed by a series of synthetic operations similar to those described above for dihydropyran (**12,** X = T).

4,4-Dimethyldihydropyrans **4, 13** (X = T), and **14** (X = T) were synthesized from 4,4-dimethylglutaric anhydride (**20b**)

Scheme II



in a fashion similar to that described for the monomethyl analogues.

Determination of Isotope Effects. The deuterium-labeled starting materials were photooxidized and the product compositions were compared with those from the undeuterated compounds. The results were expressed as a product isotope effect, defined as

$$(k_H/k_D)_{product} \equiv (\text{hydroperoxide/dioxetane})_H/(\text{hydroperoxide/dioxetane})_D \quad (1)$$

The product compositions were determined by vapor chromatography of the stable thermal conversion products, the dihydropyrone and the aldehydoformate, from **3** and **2,** respectively.

The tritium kinetic isotope effects were determined by following the T enrichment of the samples of starting material during oxidation by scintillation counting. The overall rates of oxidation were determined by measuring the oxygen uptake from a gas buret at carefully controlled temperature and pressure.

Primary D and T kinetic isotope effects are subject to the relationship[13,14]

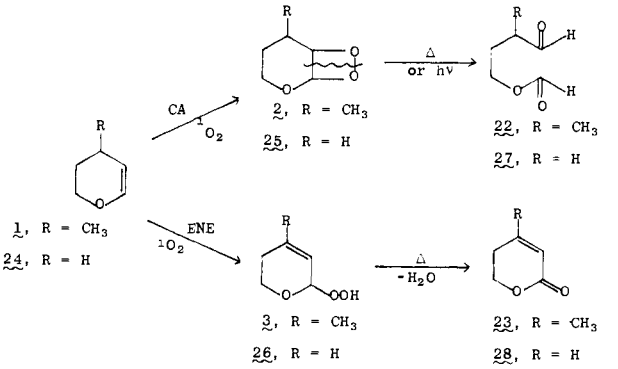
$$k_H/k_T = (k_H/k_D)^{1.442} \quad (2)$$

Familiar types of kinetic analysis[18] show that the competing reaction modes of unlabeled and tritium tracer-labeled compounds can all be treated as pseudo-first-order reactions for purposes of determining their relative rates. Thus, if P_{CA} and P_{ene} are the molar fractions of product, respectively, representing cycloaddition and ene reaction, then

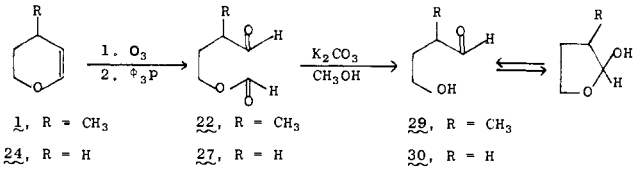
$$(k_H/k_T)_{CA} = (P_H/P_T)_{CA} \cdot (k_H/k_T)_{total}$$
$$(k_H/k_T)_{ene} = (P_H/P_T)_{ene} \cdot (k_H/k_T)_{total} \quad (3)$$

By combining the measured deuterium product isotope effects (Table II) in several solvents with the corresponding kinetic tritium isotope effects and the overall rates of oxygen consumption, the figures of Tables III and IV were arrived at. Details of the procedures are given in the Experimental Section.

Photooxidation of 1 and 4. 1. Product Study. As mentioned above, 4-methyl-2,3-dihydro-γ-pyran (**1**), upon photosensitized oxidation, is expected to yield two primary products: a cycloaddition product, dioxetane **2,** and an "ene" reaction product, allylic hydroperoxide **3.** The products actually isolated by preparative VPC are the derived aldehydoformate **22** and dihydropyrone **23. 22** and **23** were characterized by their spectra (see Experimental Section) and their identities further verified by the data given by Schaap[19] for the unmethylated analogues **27** and **28.**



Authentic samples of **22** and **27** were prepared from the ozonolysis of dihydropyrans **1** and **24,** respectively. Furthermore, deformylation of aldehydoformates **22** and **27** with



K_2CO_3 in methanol[20] yielded the corresponding 2-hydroxytetrahydrofurans (4-hydroxybutanals) **29** and **30.**

Hydroperoxides **3** and **26** are indeed stable at room temperature. **3** was isolated from the reaction mixture as a colorless crystalline solid which decomposes under VPC conditions to give a single peak corresponding to **23.**[21] Such a dehydration is not unprecedented and several examples have been cited by Gollnick.[22] In fact Schenck,[23] who had earlier studied the photosensitized oxidation of dihydropyran, reports that carefully isolated **3** can be easily dehydrated with ketene.

The dimethyl analogue of **1,** dihydropyran **4,** photooxidized smoothly to yield aldehydoformate **31** exclusively. Several attempts to isolate dioxetane **5** from the reaction mixture were unsuccessful.

It should be noted that, for the monomethyl analogue **1,** the photooxidation times needed for 50% reaction of a 130-mg sample of substrate in 1 ml of solvent were ~15 min in acetonitrile and ~30 min in benzene. For the dimethyl analogue **4,** under the same conditions, the photooxidation times needed were ~1 h and ~6 h for acetonitrile and benezene, respectively. Similarly Atkinson[24,25] reported that complete photooxidation of 6-*p*-methoxyphenyl-2,3-dihydro-γ-pyran required 1 h, while its 4,4-dimethyl analogue required 5 h. Both of these compounds photooxidize to yield dioxetane product exclusively. It would seem, then, that dioxetane formation is either hindered by the dimethyl substitution or assisted by allylic hydrogen. It is also possible that the dimethyl compounds have an independent quenching effect on singlet oxygen. However, such an effect cannot be predicted from the theory of quenching in its present state.

2. Solvent Effects. Scaap and Bartlett[26-28] studied the solvent effect on the ratio of **27** and **28,** taking this ratio as a measure of the competitive rates of 1,2 cycloaddition and ene reaction of singlet oxygen on dihydropyran. Their results indicated that this ratio varies over a 59-fold range as the solvent is changed from benzene to acetonitrile, with the polar solvents favoring the cycloaddition mode of reaction over the ene type. A similar product effect is seen in the case of **1** in Table I. The overall rate of oxygen uptake under identical illumination and sensitizer concentration also varies with solvent.

The solvent may affect the overall rate of a photosensitized oxidation in several ways. (a) It may increase the rate of excitation of the sensitizer, by exciplex absorption, or it may quench the excited sensitizer in competition with oxygen. (b) A solvent with any UV absorption of its own may screen some

Table I. Solvent Effect on the Photooxidation of 4-Methyl-2,3-dihydro-γ-pyran[a]

Solvent system	Ratio of CA/ene[b,c]	Dielectric constant	E_T[d]	O_2 uptake/h (mmHg)	Partial rate CA	Partial rate Ene	$^1O_2$ lifetime,[e] μs	Solubility of O_2 (Ostwald 1)[g]	Sensitizer,[f] 10^{-3} M
Cyclohexane	13/87 = 0.15	2.0	31.2	2.5	0.32	2.2	17		TPP (dil)
Benzene	17/83 = 0.20	2.3	34.5	11.0	1.87	9.1	24	0.223	TPP
Neat	22/78 = 0.28	5.6[h]		10.9	2.4	8.5			TPP
5:1 Benzene-CH_3OH	34/67 = 0.51			7.7	2.6	5.2	~16[i]		TPP
CS_2	40/60 = 0.67	2.6	32.6	7.2	2.9	4.3	200		TPP
2:1 CH_3OH-benzene	47/53 = 0.89			3.6	1.7	1.9			TPP
CH_3OH	60/40 = 1.50	32.6	55.5	2.1	1.3	0.8	7	0.248	RB
Formamide	64/36 = 1.78	109.5	56.6	7.6	4.9	2.7			MB
CH_3CN	84/16 = 5.25	37.5	46.0	22.2	18.6	3.6	30		MB

[a] 50 μL of substrate in 600 μL of solvent. [b] VPC peak area ratios using a 4 ft × ¼ in. aluminum column packed with 20% Carbowax 20M on Chromosorb P; oven temperature 190 °C; thermal conductivity detector; Areas evaluated by triangulation. [c] Ratios remained constant throughout duration of irradiation. [d] The values are cited from C. Reichardt, "Losungsmitteleffekte in der Organischen Chemie," Verlag Chemie, Weinheim/Bergstr., West Germany, p 162. [e] P. B. Merkel and D. R. Kearns, *J. Am. Chem. Soc.*, **94**, 1030, 7244 (1972). [f] Sensitizer concentrations are ~10^{-3} M with the exception of cyclohexane where the concentration was more dilute. TPP, tetraphenylporphyrin; MB, methylene blue; RB, rose bengal. [g] Seidell, "Solubilities of Inorganic and Organometallic Compounds", Vol. 2, 4th ed, American Chemical Society, Washington, D.C., 1965. [h] Measured directly on 2,3-dihydro-γ-pyran (dielectric constant meter designed by B. Kohler, No. EDC-347-3). [i] This value was actually calculated[e] for a 4:1 mixture of benzene and methanol.

actinic light from acting on the sensitizer. (c) The solubility of oxygen varies considerably with the solvent, and this may affect the probability of energy transfer to O_2 in competition with other quenchers. (d) Solvents quench singlet oxygen at different rates.

The solvation of later intermediates in photooxidation can vary with solvent, especially in cases of strong polarity, with consequences for rates, reversibilities, and selectivities in the steps of the process.

It is perhaps not surprising, therefore, that the gross rates of oxygen absorption do not correlate perfectly with either the lifetime of singlet oxygen in the solvent or the polarity of the latter. Over the range of solvents in Table I, no products other than **22** or **23** could be observed.

3. Product Isotope Effect Determination. The product isotope effects for γ-deuterium substitution (**10**, X = D), given in Table II, are somewhat surprising, since they indicate that in nonpolar solvents the effect of γ deuteration is small. This observation will be further discussed below.

4. Kinetic Isotope Effects. Approximately 130 mg of partially tritiated substrate in 1 mL of solvent (benzene/TPP or acetonitrile/MB) was photooxygenated as described. After the reaction had proceeded to ~50% completion, the remaining starting material was isolated by preparative vapor phase chromotography (VPC) at 70 °C on a 10-ft Apiezon J column. A sample of the recovered starting material was accurately weighed, dissolved in 10 mL of scintillation fluid and counted 14–18 times to a 0.2% 2σ statistical counting error (10^6 counts).[29,30] To measure the number of counts in the initial substrate, a 65-mg sample was dissolved in 1 mL of solvent, preparatively chromatographed, and counted as above. This procedure was adopted for two reasons. First, the substrate contained a small percentage of very "hot" impurities, easily separable by VPC. Second, it compensated for any error resulting from exchange on the column or tailing of solvent (both of which were determined to be minimal by collection–reinjection and by comparing the cpm (counts per minute) of the collected sample, injected and without solvent).

Table III lists the final results obtained by scintillation counting for the kinetic tritium isotope effects on the photooxidation of compounds **1** and **4.**

Table IV shows the values derived for tritiated compound **10** (X = T). For this compound, the tritium *product* isotope effect can be calculated by eq 2 from the corresponding experimentally determined deuterium product isotope effects. These $(k_H/k_T)_{product}$ values are listed in Table III as 2.310 in acetonitrile and 1.128 in benzene. This corresponds to 87.76%

Table II. Product Isotope Effect of γ Deuteration on the Singlet Oxygen Reaction of 4-Methyl-2,3-dihydro-γ-pyran[a]

For Benzene/TPP

	Run	Injection I	Injection II	Injection III	Av
Ratio of **23**/**22** (X = H)	A	3.177	3.256		3.217 ± 0.040
	B	3.341	3.240	3.179	3.253 ± 0.058
	C	3.108	3.058	3.010	3.059 ± 0.033
	D	2.942	2.984	2.959	2.962 ± 0.045
					Av 3.123 ± 0.114
		24.26% **22**, 75.74% **23**			
Ratio of **23**/**22** (X = D)	A	2.912	2.826	2.868	2.869 ± 0.029
	B	2.801	2.878	2.953	2.877 ± 0.051
					Av 2.873 ± 0.041
		25.82% **22**-*d*, 74.18% **23**-*d*			

Product isotope effect in benzene
$(k_H/k_D)_{product}$ = (ene/CA)$_H$/(ene/CA)$_D$ = 1.087 ± 0.055

For Acetonitrile/MB

	Run	Injection I	Injection II	Injection III	Av
Ratio of **23**/**22** (X = H)	A	0.3223	0.3177	0.3169	0.3190 ± 0.0022
	B	0.3255	0.3197	0.3162	0.3205 ± 0.0033
				Av	0.3197 ± 0.0028
		75.77% **22**, 24.23% **23**			
Ratio of **23**/**22** (X = D)	A	0.1764	0.1764	0.1819	0.1782 ± 0.0024
	B	0.1772	0.1863	0.1754	0.1796 ± 0.0044
				Av	0.1789 ± 0.0034
		84.83% **22**-*d*, 15.17% **23**-*d*			

Product isotope effect in acetonitrile
$(k_H/k_D)_{product}$ = (ene/CA)$_H$/(ene/CA)$_D$ = 0.3197/0.1789 = 1.787 ± 0.050

[a] Runs were carried out on an HP-7620 chromatograph with flame ionization and automatic integrator.

dioxetane and 12.24% hydroperoxide in acetonitrile and 26.54% dioxetane and 73.46% hydroperoxide in benzene.

Discussion

Any suggested mechanism for these reactions must take into account the following observations.

(1) In the photooxidation of enol ethers,[31] polar solvents favor cycloaddition while nonpolar solvents favor ene product

Table III. Isotope Effects on the Photooxidation of 4-Methyl-2,3-dihydro-γ-pyran (**1**)

Compd	Quantity	Value in Acetonitrile/MB	Value in Benzene/TPP
1	Product composition	75.77/24.23[a]	24.26/75.74[a]
10 (X = D)	Product composition	84.83/15.17[a]	25.82/74.18[a]
	$(k_H/k_D)_{product}$[b]	1.787 ± 0.050 (2.310)[c]	1.087 ± 0.055 (1.128)[c]
10 (X = T)	$(k_H/k_T)_{kinetic}$	1.211 ± 0.017 (1.142)[d]	1.335 ± 0.023 (1.222)[d]
11 (X = T)	$(k_H/k_T)_{kinetic}$	0.866 ± 0.003 (0.905)[d]	0.908 ± 0.006 (0.935)[d]
12 (X = T)	$(k_H/k_T)_{kinetic}$	1.067 ± 0.010 (1.046)[d]	0.980 ± 0.010 (0.986)[d]
13 (X = T)	$(k_H/k_T)_{kinetic}$	0.897 ± 0.006 (0.927)[d]	0.897 ± 0.002 (0.927)[d]
14 (X = T)	$(k_H/k_T)_{kinetic}$	1.001 ± 0.015 (1.001)[d]	0.994 ± 0.007 (0.996)[d]
4	Product composition	100[e]	100[e]

[a] Percent dioxetane/percent hydroperoxide based on VPC peak area ratios using flame ionization detector. [b] $(k_H/k_D)_{product}$ = (hydroperoxide/dioxetane)$_H$/(hydroperoxide/dioxetane)$_D$. [c] Corresponding calculated k_H/k_T values. [d] Corresponding calculated k_H/k_D values. [e] Percent dioxetane.

Table IV. Calculation of $(k_H/k_T)_{CA}$ and $(k_H/k_T)_{ene}$ for 4-Methyl-2,3-dihydro-γ-pyran-*4-t*

	Acetonitrile	Benzene
$(k_H/k_T)_{total}$	1.211	1.335
$(P_H/P_T)_{CA}$	75.77/87.76 = 0.8634	24.26/26.54 = 0.9141
$(k_H/k_T)_{CA}$	1.046	1.220
$k_H/k_D)_{CA}$	1.032	1.148
$(P_H/P_T)_{ene}$	24.23/12.24 = 1.980	75.74/73.46 = 1.031
$k_H/k_T)_{ene}$	2.397	1.376
$(k_H/k_D)_{ene}$	1.834	1.248

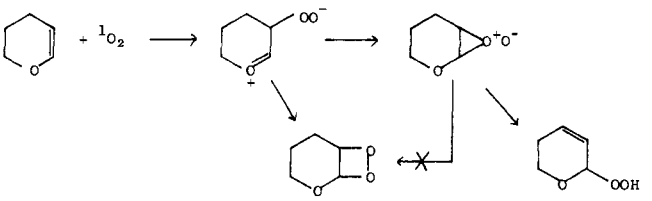
formation. The solvent effect on the ratio of ene to cycloaddition is, nevertheless, much smaller than those seen in ionic reactions (a 34-fold effect in going from cyclohexane to acetonitrile in the case of compound **1**, and a 7-fold effect in going from benzene to acetonitrile in the case of 1-methoxycyclohexene[31]). Furthermore, in the competition of two symmetrically substituted molecules, one undergoing only ene reaction (tetramethylethylene) and the other only cycloaddition (*cis*-diethoxyethylene), there is little if any solvent dependence.[26,27] Hence, this solvent effect seems to be associated with the unsymmetrical character of the enol ether substrate, or a branching reaction path.

(2) The product isotope effect (1.787) for compound **10** (X = D) in acetonitrile indicates that allylic hydrogen abstraction by oxygen becomes relatively more difficult as a result of deuterium substitution; hence, dioxetane product is favored. In benzene, however, despite the fact that ene reaction predominates, only a negligible product isotope effect is observed (1.087).

Dewar[32a] has suggested on theoretical grounds that the photooxidation of enol ethers proceeds via an initial formation of an extended zwitterion which can in turn proceed directly to dioxetane or alternatively to ene product via a perepoxide (Scheme III). This scheme embodies some of the features required by the experimental results,[32b] but Dewar's assignment of a sequence of steps does not provide for the product isotope effect seen in acetonitrile. For this the γ hydrogen must be allowed to contribute to the choice between ene product and dioxetane.

(3) Substitution of a deuterium on a carbon undergoing rehybridization from sp^2 to sp^3 produces an inverse isotope effect (i.e., $k_H/k_D < 1.0$) with a k_H/k_D of ~0.9.[33] The kinetic isotope effects measured for the β position, 5, of compounds **1** and **4** indicate that, in both benzene and acetonitrile, substantial rehybridization from sp^2 to sp^3 has occurred in the trnasition state. Furthermore, the data demonstrate that, in both ene reaction and dioxetane formation, position 5 undergoes rehybridization and is very much involved in the transition state. *The simplest concerted ene mechanism is, therefore, clearly ruled out in the photooxidation of these enol ethers.*

Scheme III



(4) On the other hand, the kinetic isotope effects for the α-position 6 of compounds **1** and **4** indicate that in the transition state no appreciable rehybridization occurs at position 6 in acetonitrile and little, if any, in benzene. With respect to compound **1**, it is "ene" product that predominates in benzene, and, consequently, *isotope effects at position 6, as well as those at 5, speak against the concerted mechanism, at least for these enol ethers.* The numbers do not rule out the possibility of a perepoxide as an intermediate on the way to product formation.

(5) The inverse (i.e., $k_H/k_D < 1.0$) secondary isotope effects observed for compounds **11** and **13** in acetonitrile recall other [2 + 2] cycloadditions were one end of a double bond shows an inverse effect, while the other shows a normal effect. Koerner Von Gustorf et al.[34] reported that, in the cycloaddition of azodicarboxylates with vinyl ethers, the position α to the ether oxygen shows a normal secondary isotope effect (k_H/k_D = 1.12), while the β position shows an inverse effect (k_H/k_D = 0.83). Similarly, Baldwin and Kapecki[35] reported that, in the addition of diphenylketene to deuteriostyrenes, secondary effects for the reaction are k_H/k_D = 0.91 at the β position and 1.23 at the α position of styrene at 65 °C. This is normal expectancy for a stepwise cycloaddition, but does not exclude unsymmetrical concerted addition such as has been proposed for both ketene[7,37] and singlet oxygen.[26,28,38,29] Concertedness does not imply identical degrees of bond formation at dissimilar sites in the transition state.

It is also significant that dioxetane formation seems to proceed faster as solvent polarity is increased. As noted above, the photooxidation of **4** in benzene with TPP took six times longer than it did in acetonitrile with methylene blue. We have also studied the rate of photooxidation of **4** in several other solvents and the results are listed in Table V. In a common solvent, chloroform, MB and TPP afford nearly the same rate of oxygen uptake, but the TPP-sensitized reaction is 3.6 times faster in chloroform than in benzene. The rate of photooxidation is better correlated with solvent polarity than with the singlet oxygen lifetimes for the given solvents.[40]

Ketene additions show a similar effect. Huisgen and Otto[41] have studied the dimerization of dimethylketene and reported that the rate of reaction increased 30-fold in going from carbon tetrachloride to acetonitrile. They conclude that, while the reaction is probably concerted, there is unequal bond formation and partial charge separation in the transition state.[42]

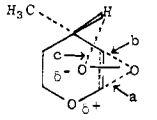
(6) The kinetic isotope effect for position 4, as seen from Table III, is rather small for a primary effect, especially in benzene. Similar results have been observed by other workers in the field.[44,45] It has been considered[44-48] that these low numbers can be explained if we assume an early product-forming transition state such as can occur when one of the reactants is in an excited state.

The isotope effects at position 5, through small, are quite consistent and are of the order of magnitude to be expected for substantial rehybridization to sp^3 at the transition state.

Conclusions

The detailed significance of kinetic and product isotope effects depends upon whether, and how, an intermediate occurs during the reaction. It would be very desirable to have compelling evidence on this point, since both the dioxetane and allylic hydroperoxide could in principle be formed in independent, symmetry-allowed concerted processes and yet could also arise in competing reactions of an intermediate. The isotope effects themselves are not capable of distinguishing between the different mechanistic cases, but they impose different restrictions on the formulation of the mechanism according to which case is adopted as a framework for analysis.

Formula **32** serves to depict the interactions a, b, and c indicated by the kinetic tritium isotope effects. In the case of



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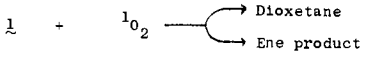
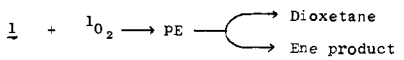
independent concerted processes, neither transition state lies on the direct "least motion" path from reactants to products: the k_H/k_T values of Table III for dioxetane formation alone



show a seemingly irrelevant involvement of the γ-hydrogen atom. If this is a concerted $[2_s + 2_a]$ reaction, it deviates from the simplest geometry not only in the strong ionic contribution to the O-C$^\alpha$ bond but in a hydrogen-bonding interaction between that same oxygen and H$^\gamma$. The transition state leading to ene product is still farther from its simplest abstraction, in that the C-O bonding detectable from the isotope effects is to C$^\beta$, whereas in the product the bonding is to C$^\alpha$.

An alternative framework for viewing the isotope effects is the irreversible formation of a perepoxide (PE), which is then partitioned rapidly between dioxetane and ene product in competing rearrangements. Skepticism of the perepoxide hypothesis has increased because several extensions of it have not stood the test of further experiment. For example, the perepoxide of biadamantylidene is not intercepted by pinacolone,[49a] and the epoxides that sometimes accompany dioxetanes in photosensitized oxidation do not have a common origin with the dioxetane.[49a,b]

In the case assuming perepoxide, the kinetic tritium isotope effects observed experimentally (α, 0.994 ± 0.007; β, 0.908



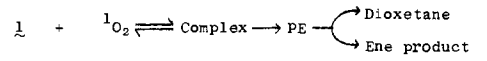
± 0.006; γ, 1.335 ± 0.034 in benzene) are the ones that apply to the direct process of perepoxide formation. The three-membered ring of the intermediate is then viewed as perturbed only by the strong donor character of the enol-ether carbon atom, which makes its contribution to the perepoxide ring relatively ionic. If the perepoxide is an intermediate, bonding to C$^\beta$ on the way to ene product no longer presents a problem. The interaction c, not required in the simplest formulation of the perepoxide, is rationalized as a favoring feature for the negative O of the perepoxide; it also indicates a preference for perepoxide formation in the configuration shown (O_2 trans to methyl), and fits with the slower oxygenation of the dimethyldihydropyran **4** compared to **1**. Finally, if the kinetic isotope effects apply directly to the formation of perepoxide, the higher value of the interaction c in benzene (1.335) than in acetonitrile (1.211) reflects the greater dependence of the transition state on intramolecular charge accommodation in the less polar solvent.

Table V. Relative Rates of Photooxidation for 4,4-Dimethyl-2,3-dihydro-γ-pyran (**4**)

Solvent	Sensitizer	K_{rel}	Polarity parameter, E_T[a]	O_2 lifetime,[b] μs
C_6H_6	TPP	1	34.5	24
THF	TPP	1.6	37.5	
$CHCl_3$	MB	3.1	39.1	60
$CHCl_3$	TPP	3.6	39.1	60
CH_3CN	MB	6.0	46.0	30

[a] See Table I, footnote *d*. [b] Reference 40.

These two cases do not, of course, exhaust the possibilities. One might refer interaction c to an initial charge-transfer complex between **1** and singlet oxygen, and conclude that the



perepoxide itself need not experience interaction c at all.

Thus the isotope effects can be used to yield a description of the reaction as either two independent concerted processes or a reaction by way of a common intermediate, but only in the latter case do the transition states appear to lie on a direct path from reactants to products.

Experimental Section

NMR spectra were obtained on Varian A-60, T-60, and HA-100 spectrometers. In reporting the data, the values obtained using the HA-100 spectrometer are asterisked. Infrared spectra were taken with a Perkin-Elmer Model 137 spectrometer. Mass spectra were run on an Associated Electrical Industries, Ltd. Model MS-9 mass spectrometer. Elementary analyses were performed by Anacon Associates (Chelmsford, Mass.). Vapor phase chromatograms were run with Hewlett-Packard F & M Models 700 and 7620, Varian Aerograph Models 90-P3, and Autoprep Model A-700. Peak areas were measured by a disk integrator, triangulation, and Hewlett-Packard digital integrator. Scintillation counting was done in a Beckman LS-250 liquid scintillation system. Ozone was generated in a Welsbach Corporation ozonator Model T-23 (2-4% ozone in oxygen).

3-Hydroxybutyraldehyde-3-*t* Dimethyl Acetal (16, X = T). A slurry of 3.15 g (0.075 mol) of lithium aluminum hydride ($LiAlH_4$) in 100 mL of dry ether was placed in a 300-mL 3-neck round-bottom flask topped with a condenser, a pressure equalizing dropping funnel, and a stopper. The condenser in turn was topped with a nitrogen inlet tube and a nitrogen blanket was maintained throughout the reaction. After the slurry had been stirred magnetically for 15 min, 1.66 mg of tritiated $LiAlH_4$ (5 mCi, New England Nuclear) was added. A solution of 32.1 g (0.25 mol) of distilled acetylacetaldehyde dimethyl acetal (**15**) (Aldrich; bp 86-88 °C (30 mm), 65-67 °C (13 mm); lit. bp 70-73 °C (20 mm)[50]) in 100 ml of dry ether was added dropwise from the dropping funnel over a period of 45 min as gentle refluxing was maintained. The solution was stirred for an additional 2 h and then hydrolyzed by successive dropwise addition, with vigorous stirring, of 3.2 g of water, 3.2 g of 15% aqueous sodium hydroxide solution, and 9.6 g of water.[51] The solution was magnetically stirred for another 45 min and gravity filtered. The salts were washed with ether several times and the combined ether washings were evaporated under reduced pressure to yield 33.4 g (0.25 mol, 100% yield) of colorless product **16**. Scintillation counting indicated a count of 1.7×10^8 cpm/mol. VPC analysis[52] (oven 130 °C) showed only product **16** (retention time 6 min) and no detectable amount of ketone **15** (retention time 4 min).

3-Hydroxybutyraldehyde Dimethyl Acetal (16, X = H). Compound **16** distilled at 77–78 °C (12 mm): NMR (CCl_4) δ* 1.13 (3 H, d, J = 6 Hz), 1.63 (2 H, m), 2.76 (1 H, s), 3.26 (3 H, s), 3.28 (3 H, s), 3.82 (1 H, sextet), 4.47 (1 H, t, J = 6 Hz); IR (CCl_4) 3509 (m), 2927 (s), 2805 (m), 1433 (m), 1400 (m), 1356 (m), 1268 (w), 1228 (w), 1186 (m), 1116 (s), 1066 (s), 1051 (s), 958 (m), 940 (m), 915 (w), 852 (w) cm^{-1}.

3-Hydroxybutyraldehyde-*3-d* Dimethyl Acetal (16, X = D). The procedure was identical with that used for the tritiated analogue except that lithium aluminum deuteride (ICN) was used instead of $LiAlH_4$ and $LiAlT_4$. The product distilled at 83–84 °C (20 mm): NMR (CCl_4) δ* 1.12 (3 H, s), 1.62 (2 H, d, J = 6 Hz), 2.88 (1 H, s), 3.25 (6 H, 2 s separated by <2 Hz), 4.45 (1 H, t, J = 6 Hz); IR (CCl_4) 3461 (s), 2926 (s), 2805 (s), 2119 (w), 1434 (s), 1426 (m), 1382 (s), 1361 (s), 1291 (m), 1239 (w), 1195 (s), 1122 (s), 1047 (s), 965 (m), 940 (s), 876 (m) cm^{-1}.

Crotonaldehyde-*3-t* (17, X = T).[9] A three-necked 50-ml round-bottom distilling flask, topped with Claisen head with a 50-ml pear-shaped receiver, a graduated dropping funnel, and a stopper, was charged with 3 g of anhydrous oxalic acid and 450 mg of hydroquinone. The system was evacuated to 3–5 mmHg and the pressure was maintained at that level with a manostat. To prevent loss of product, the receiver was cooled in liquid nitrogen and a second trap was placed between the system and the manostat. The distilling flask was immersed in an oil bath maintained at 75 °C. 26 g (0.194 mmol) of 3-hydroxybutanal-*3-t* dimethyl acetal (**16**, X = T) was added from the dropping funnel over a period of 14 h. The solution was magnetically stirred throughout the addition and for another hour after the addition had been completed. The crotonaldehyde and methanol distilled over as they were formed to yield 23 g of product. VPC analysis[52] (oven 140 °C) showed almost no starting material and an approximate ratio of 2:1 methanol to crotonaldehyde.

The product was separated from the methanol by standing for 1 h with 50 g of molecular sieves 4A, extraction with Freon 11, and distillation with a 1-ft Vigreux column.

Bulb-to-bulb distillation at room temperature and high vacuum gave 5 g of product (0.07 mol or a 36% yield based on pure crotonaldehyde). Although the VPC analysis showed only one peak, NMR indicated the presence of about 30% of crotonaldehyde dimethyl acetal: δ 1.75 (d), 3.2 (s), 4.7 (d), 5.7 (m). Attempts to distill out the crotonaldehyde led to polymerization, and, hence, the product mixture was used without further purification. The only effect was a reduced yield in the next step of the synthesis.

Crotonaldehyde (17, X = H). The unlabeled aldehyde was obtained from Eastman.

Crotonaldehyde-*3-d* (17, X = D). The deuterium analogue was prepared as described above from 3-hydroxybutanal-*3-d* dimethyl acetal (**16**, X = D). The NMR spectrum shows a singlet at δ 3.2 that cannot be attributed to **17**, but is probably due to crotonaldehyde-*3-d* dimethyl acetal: NMR (CCl_4) δ* 2.0 (3 H, s), 6.02 (1 H, m), 9.4 (1 H, d, J = 8 Hz). In addition, a large (~2 H relative to CH_3) singlet was present at δ 3.2 and minor peaks at 1.75, 4.65, and 5.25. The absence of detectable absorptions at 6.75 indicates complete γ deuteration.

2-*n*-Butoxy-4-methyl-2,3-dihydropyran (18, X = H).[8] A solution of 6.75 g (0.096 mol) of freshly distilled commercial crotonaldehyde, 0.4 g of hydroquinone, and 12.04 g (0.12 mol) of freshly distilled vinyl *n*-butyl ether was sealed under reduced pressure in an 18 mm × 54 cm heavy-walled Pyrex tube. The tube was heated at 200 °C for 18 h and allowed to cool to room temperature and the contents were transferred to a distilling flask with the aid of ~5 ml of pentane. After removal of the pentane, distillation under reduced pressure was attempted but this operation was thwarted by excessive foaming. GLC analysis[52] (oven 125 °C) of the residue, 16.40 g, showed the material to consist of 93.5% of the desired isomeric dihydropyrans (**18**, X = H) (retention times 3.6 and 4.6 min) and 6.5% of several low boiling components. This material was used without further purification in the succeeding step of the sequence. A sample for spectral analysis was isolated by preparative VPC (6 ft × 1/4 in. Carbowax 20M on 60/80 Chromosorb P): NMR (CCl_4) δ 1.0 (6 H, m), 1.5 (5 H, m), 1.9 (1 H, m), 2.3 (1 H, m), 3.4 (1 H, m), 3.75 (1 H, m), 4.8 (1 H, t, J = 5 Hz), 6.05 (1 H, dt).

2-*n*-Butoxy-4-methyl-*4-d*-2,3-dihydropyran (18, X = D). The procedure was identical with that used for the protium compound **18** (X = H) except for quantities and workup. From 4.04 g (0.057 mol) of **17** (X = D) and 7.52 g (0.075 mol) of vinyl *n*-butyl ether there was obtained 11.43 g of product mixture. Unlike the case with the protium analogue, there were many low boiling impurities besides solvent. Successive reduction of the pressure to 14 mm followed by vacuum transfer at mechanical pump pressure afforded 7.71 g of a colorless liquid, shown by GLC to contain 6.25 g (54%) of the desired isomeric cycloadducts, **18** (X = D). This material was used without further purification in the hydrogenation step, but a pure sample of **18** (X = D) was obtained by preparative VPC for spectral analysis: NMR (CCl_4) δ* 1.0 (6 H, m), 1.5 (6 H, m), 1.9 (1 H, m), 3.4 (1 H, m), 3.75 (1 H, m), 4.5 (1 H, m), 4.8 (1 H, m), 6.07 (1 H, t, J = 6 Hz).

2-*n*-Butoxy-4-methyl-2,3-dihydro-γ-pyran-*4-t* (18, X = T). A mixture of 24 g (0.34 mol) of crotonaldehyde (2.4 g of tritiated analogue prepared in the previous step and 21.6 g of commercially available protium compound), 36 g (0.35 mol) of vinyl *n*-butyl ether, and 0.5 g of hydroquinone was sealed under reduced pressure in a heavy-walled Pyrex Carius tube. The tube was heated at 200 °C for 17 h and allowed to cool to room temperature. While the product obtained when using only commercial crotonaldehyde was yellow, the product in this case had an amber color. VPC analysis[52] (oven 125 °C) showed, in addition to the desired product, several other lower boiling compounds. The product was distilled at 60–85 °C at 8–10-mm pressure into a liquid N_2 cooled receiver to give 17.5 g of crude 2-*n*-butoxy-4-methyl-2,3-dihydro-γ-pyran-*4-d* (**18**, X = T). The material, though still containing impurities, was used without further purification in the hydrogenation step.

2-*n*-Butoxy-4-methyltetrahydropyran (19, X = H). A mixture of 15.22 g (0.089 mol) of **18** (X = H) and 0.4 g of 5% Pd/C was hydrogenated in the Parr apparatus with a starting pressure of 41.5 psi. After 2 h the pressure had fallen to 34.0 psi and there was no further pressure drop during the succeeding 0.75 h. The catalyst was removed by filtration and washed thoroughly with pentane. These washings were collected separately from the initial filtrate. After removal of the pentane, the combined filtrates were subjected to high vacuum bulb-to-bulb distillation to afford 12.24 g (80%) of **19** (X = H) as a colorless liquid, shown by VPC[52] (oven 125 °C) to be 93% desired isomeric tetrahydropyrans (retention times 3.6 and 5.4 min) and 7% low boiling impurities. This material was used without further purification in the succeeding step. A sample of the isomer with the longer retention time was isolated by preparative VPC for spectral analysis: NMR (CCl_4) δ* 0.95 (6 H, m), 1.5 (9 H, m), 3.3 and 3.8 (4 H, 2 m), 4.18 (1 H, dd).

2-*n*-Butoxy-4-methyl-*4-d*-tetrahydropyran (19, X = D). The procedure used was identical with that described for the protium analogue except for quantities and workup. From 7.05 g of crude **18** (X = D), 6.95 g of crude **19** (X = D) was obtained. The low boiling impurities were removed by distillation through a modified Claisen still by gradually reducing the pressure until a small forerun of bp 75 °C (6 mm) was obtained. VPC showed that the residue, 4.01 g (71%), was 98% pure **19** (X = D). This material was used without further purification in the succeeding step.

2-*n*-Butoxy-4-methyltetrahydropyran-*4-t* (19, X = T). Tritiated compound **18** (17.5 g) was combined with 50 g of the protium analogue and hydrogenated with 0.5 g of 5% Pd/C in a Parr apparatus under 50 psi. VPC analysis showed almost complete hydrogenation. The material, **19** (X = T), was used without any further purification.

4-Methyl-2,3-dihydropyran (1 or 10, X = H). A 50-ml distillation flask, topped with a modified Claisen head with receiver, was charged with 6.16 g (0.036 mol) of **19** (X = H) and a catalytic amount of P_2O_5. The flask was immersed in an oil bath at 155 °C and the temperature of the bath was quickly raised to 185 °C. The product began to distill at once and 5.28 g of material, bp 105–108 °C, was collected in an iced receiver containing 0.12 g of anhydrous sodium carbonate. The reaction was repeated with an additional 4.87 g of **19** (X = H) and the combined distillates were treated with 1.7 g of sodium metal shot, added one piece at a time. The resulting mixture was heated under reflux for 0.5 h and worked up by vacuum transfer to afford 4.80 g (96%) of **1** which was shown by GLC to be >99% pure. A portion of this material was distilled from sodium at atmospheric pressure to afford 2.01 g of **1**, bp 100–101 °C. The remainder of the material was recovered by vacuum transfer. The spectral and VPC properties of these samples were identical and the latter was used in the photooxygenation experiments: NMR (CCl_4) δ* 1.02 (3 H, d, J = 8 Hz), 1.46 (1 H, m), 1.87 (1 H, m), 2.23 (1 H, m), 3.88 (2 H, m), 4.45 (1 H, dd), 6.18 (1 H, dd); IR (film) 3110 (w), 2980 (s), 2988 (s), 1645 (s), 1464 (m), 1452 (m), 1436 (w), 1400 (w), 1310 (w), 1306 (w), 1232 (s),

1164 (m), 1114 (m), 1100 (w), 1070 (s), 1049 (w), 1007 (m), 993 (w), 981 (w), 966 (w), 914 (m), 856 (s).

4-Methyl-2,3-dihydro-γ-pyran-*4-d* (10, X = D). The procedure was essentially identical with that used for the protium analogue except for quantities. From 4.01 g of **19** (X = D), 3.62 g of **10** (X = D) was obtained as a colorless liquid, shown by GLC to be >99% pure: NMR (CCl_4) δ* 1.02 (3 H, s), 1.5 (1 H, m), 1.85 (1 H, m), 3.85 (2 H, m), 4.24 (1 H, d, J = 6 Hz), 6.10 (1 H, d, J = 6 Hz) (no trace of a signal at δ 2.22 was observed, even at maximum output, which indicated essentially complete deuteration at the γ position); IR (film) 3079 (w), 2939 (s), 2869 (s), 2129 (w), 1647 (s), 1464 (m), 1452 (m), 1438 (m), 1399 (w), 1379 (w), 1332 (w), 1260 (s), 1238 (s), 1144 (w), 1124 (w), 1070 (s), 1047 (w), 1002 (s), 938 (s), 870 (s), 862 (s), 815 (m), 742 (s), 733 (s).

4-Methyl-2,3-dihydro-γ-pyran-*4-t* (10, X = T). A 250-mL round-bottom flask, topped with a modified Claisen head with a 100-mL receiver, was charged with 68 g of **19** (X = T) (from the previous step) and a catalytic amount of P_2O_5 and placed in a silicon oil bath at 150 °C. The temperature was then quickly raised to 175 °C (at which distillation began) and them maintained at 185 ± 5 °C for the duration of the distillation. The distillate (34 g) boiling in a range of 100–130 °C was collected in an iced receiver.

To remove the 1-butanol formed in the course of the reaction, ~6 g of sodium shot was added, one piece at a time, to the iced receiver. The receiver was then fitted with a reflux condenser and heated for an hour in an 85 °C oil bath. The product was bulb to bulb distilled away from the sodium salts formed under high vacuum. VPC analysis showed only a trace of 1-butanol remaining. The product, **10** (X = T), was further distilled at atmospheric pressure from sodium to afford 12 g of >99% pure product, bp 101–102 °C.

Preparation of Tritium-Rich 4-Methyl-2,3-dihydro-γ-pyran-*6-t* (12, X = T). A. 3-Methyl-δ-valerolactone (21).[10] Sodium (90 g, 3.9 mol) was placed in a 2-L three-necked flask fitted with a reflux condenser (topped with drying tube), a mechanical stirrer, and a liter dropping funnel. Into the dropping funnel 64 g (0.5 mol) of 3-methylglutaric anhydride dissolved in 600 mL of absolute ethanol was added. This alcoholic solution was let into the flask as quickly as possible (10 min). The solvent continued to reflux without heating for another 15 min. Heat was then applied to keep the solution refluxing for 7 h more. Water (600 mL) was slowly added as the ethanol was distilled off. The solution was allowed to cool and 400 mL of concentrated HCl was added. The solution was continuously extracted for 12 h with ether in a Kutscher–Steudel apparatus. The ether extract was dried over a 3:1 mixture of $MgSO_4$ and $KHCO_3$. The solvent was removed under reduced pressure and the residue distilled and then redistilled (20 mm, 110–115 °C) to give 13 g (0.11 mol) of pure lactone: yield, 23%; NMR (CCl_4) δ 1.04 (3 H, d), 1.0–2.9 (5 H, m), 4.33 (2 H, m); IR (CCl_4) 2970 (m), 1747 (s), 1467 (w), 1446 (w), 1433 (w), 1394 (m), 1372 (m), 1304 (w), 1278 (w), 1254 (m), 1223 (m), 1187 (w), 1146 (m), 1089 (m), 1080 (w), 1027 (m), 912 cm^{-1}.

B. 2-Hydroxy-4-methyltetrahydropyran-*2-t*.[11] 3-Methyl-δ-valerolactone (**31**, 10.8 g, 94.6 mmol) was dissolved in 65 mL of dry ether and placed in a 300-mL three-necked round-bottom flask fitted with a reflux condenser (topped with drying tube) and a dropping funnel. The reaction was carried out under nitrogen. The solution was magnetically stirred and cooled in an ice–water–salt mixture to about −10 °C. $LiAlH_4$ (1.14 g, 30 mmol) in 75 mL of dry ether was added over a period of 35 min. After 25% of the $LiAlH_4$ had been added, a sample of tritium-rich $LiAlH_4$ (5mCi, New England Nuclear) was added through the side arm. The solution was stirred for another 3 h and allowed to warm gradually to room temperature.

To the solution 1.5 mL of water, 1.5 mL of 15% NaOH and then 4.5 mL of water were successively added. The solution was stirred for another 15 min yielding a white salt. The ether solution was filtered, dried over $MgSO_4$, and filtered again. The solvent was finally removed under reduced pressure to give 7.5 g of crude product.[51]

C. 4-Methyl-2,3-dihydro-γ-pyran-*6-t* (12, X = T). The crude product from the previous step was placed in a 25-mL round-bottom flask with a catalytic amount of TsOH. Distillation at 20 mm and an oil bath temperature of 120–150 °C gave a colorless product. The receiving flask was cooled with dry ice–acetone. The distillate was separated from the water formed and stored in the refrigerator over molecular sieves 4A in an aluminum foil covered round-bottom flask. Under these conditions the dihydropyran remained colorless. The yield was 3.5 g (35.7 mmol) or 38%.

4-Methyl-2,3-dihydro-γ-pyran-*6-d* (12, X = D). The procedure was identical with that used for the tritium analogue except for the quantities and for the use of $LiAlD_4$ (ICN). NMR (CCl_4) showed δ 1.02 (3 H, d), 1.0–2.4 (3 H, m), 3.95 (2 H, m), 4.50 (br s, 1 H). Absence of any signal at 6.10-even at maximum output—indicates essentially complete deuteration at γ position.

Preparation of Tritium-Rich 4-Methyl-2,3-dihydro-γ-pyran-*5-t* (11, X = T).[53,54] To a stirred solution of 4.4 g (44.8 mmol) of 4-methyl-2,3-dihydro-γ-pyran in 3.5 mL of ether, 2 mL of tritium-rich water (250 μCi/mL) and 4.5 drops of concentrated HCl were successively added and the solution was magnetically stirred for 48 h. The yellowish ether layer was then separated from the aqueous layer and the latter extracted twice with ether. The ether extracts were combined, dried over K_2CO_3, filtered, and concentrated under reduced pressure. The remaining yellow liquid was placed in a 50-mL round-bottom flask with a trace of *p*-toluenesulfonic acid and distilled (with foaming) at 20 mm and an oil bath temperature of 120–150 °C to give a colorless product. The receiving flask was cooled with dry ice–acetone. The water produced in the reaction was taken up by molecular sieves 4A. The yield was 2.7 g (61%).

4-Methyl-2,3-dihydro-γ-pyran-*5-d* (11, X = D). The procedure was identical with that used for the tritium analogue. After five exchanges NMR showed almost 80% deuterium incorporation: NMR ($CDCl_3$) δ 0.99 (3 H, d, J = 7 Hz), 0.85–2.5 (5 H, m), 3.93 (2 H, m), 6.30 (1 H, br s). Peaks near δ 4.55 are almost absent.

3,3-Dimethyl-δ-valerolactone.[10] Sodium (126 g, 5.5 mol) was placed into a 2-L, three-neck flask fitted with a reflux condenser (topped with drying tube), a mechanical stirrer, and a liter dropping funnel. Into the dropping funnel, 100 g of 3,3-dimethylglutaric anhydride dissolved in 900 mL of warm absolute ethanol was added. This alcoholic solution was let into the flask as quickly as possible (25 min). Heat was then applied and the solution was allowed to reflux overnight. Water (900 mL) was slowly added as the ethanol distilled off. The solution was allowed to cool and then acidified with 450 mL of concentrated HCl (pH 1). The solution was extracted four times with a total 900 mL of ether, washed with 500 mL of water, and dried over a 3:1 mixture of $MgSO_4$ and $KHCO_3$. The solvent was removed under reduced pressure and the residue distilled (20 mm, 118–122 °C) to give 22 g (0.17 mol) of pure lactone: yield 25%; NMR ($CDCl_3$) δ 1.08 (6 H, s), 1.67 (2 H, t, J = 6 Hz), 2.32 (2 H, s), 4.36 (2 H, t, J = 6 Hz); NMR (CCl_4) δ 1.09 (6 H, s), 1.67 (2 H, t, J = 6 Hz), 2.22 (2 H, s), 4.29 (2 H, t, J = 6 Hz); IR (CCl_4) 2919 (m), 1754 (s), 1456 (w), 1393 (m), 1360 (w), 1341 (w), 1305 (w), 1248 (s), 1217 (s), 1170 (m), 1137 (w), 1114 (w), 1083 (s), 1070 (m), 1041 (w) cm^{-1}.

4,4-Dimethyl-2,3-dihydro-γ-pyran (4).[11] 3,3-Dimethyl-δ-valerolactone (6.4 g) was dissolved in 65 mL of dry ether and placed in a 300-mL three-neck round-bottom flask fitted with a reflux condenser (topped with drying tube) and a dropping funnel. The reaction was carried out under nitrogen, and the reaction mixture was stirred magnetically and cooled in an ice–water–salt mixture to about −10 °C. $LiAlH_4$ (0.60 g, 15.8 mmol) in 75 mL of dry ether was added over a period of 20 min. The solution was then stirred for another 3 h as it was allowed to warm gradually to room temperature.

The reaction mixture was worked up as suggested by Fieser and Fieser.[51] To this solution 0.7 mL of H_2O, 0.7 mL of 15% NaOH solution, and then 2.1 of H_2O were successively added. The solution was stirred for another 15 min, yielding a white salt which was filtered off. The ether solvent was removed under reduced pressure to give 5.3 g of crude product.

The crude product was placed in a 50-mL round-bottom flask with a catalytic amount of *p*-toluenesulfonic acid. Distillation at 20 mm as the oil bath temperature was gradually raised from 130 to 200 °C (major fraction of 160 °C) gave a colorless product of two phases. The receiving flask was cooled in ice–water. The desired product was pipetted away from the water formed (0.65 mL) to give 3.6 g of dihydropyran **4** (0.032 mol) in 64% yield. The dihydropyran was stored in the refrigerator under argon and over molecular sieves 4A in an aluminum foil covered round-bottom flask: bp 112–114 °C (760 mm); NMR ($CDCl_3$) δ 1.03 (6 H, s), 1.63 and 3.95 (2 H, t, J = 5 Hz), 4.50 and 6.17 (1 H, d, J = 6 Hz); NMR (CCl_4) δ 1.03, 1.58, 3.88, 4.40, 6.14; IR (CCl_4) 2912 (s), 1607 (s), 1453 (m), 1395 (w), 1357 (w), 1235 (s), 1177 (w), 1158 (m), 1125 (w), 1109 (w), 1071 (s), 1029 (m), 1000 (m), 928 (m), 901 (m), 849 (m) cm^{-1}.

Preparation of 4,4-Dimethyl-2,3-dihydro-γ-pyran-*4-d* (13, X = D). The procedure was essentially the same as used for the tritiated analogue. After the initial exchange using triethylamine and D_2O, the base and water were distilled off and fresh Et_3N and D_2O added and

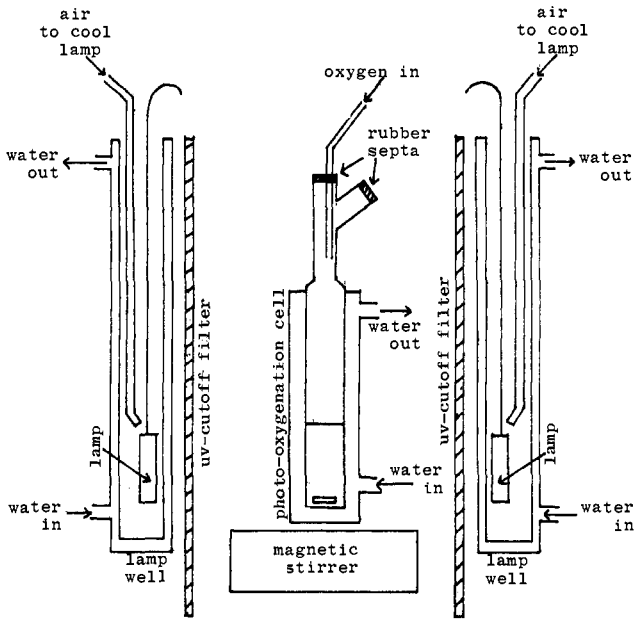


Figure 1. Photooxygenation apparatus.

the procedure was repeated. After six such exchanges the NMR showed a 93% deuterium incorporation in the lactone α to the carbonyl. Reduction and elimination gave the deuterated dihydropyran with a 95% deuterium content. Lactone-*d*: NMR (CCl_4) δ 1.10 (6 H, s), 1.69 (2 H, t, J = 6 Hz), 4.29 (2 H, t, J = 6 Hz). **13** (X = D): NMR (CCl_4) δ 1.06 (6 H, s), 1.61 and 3.90 (3 H, t), 6.15 (1 H, s).

Preparation of Tritium-Rich 4,4-Dimethyl-2,3-dihydro-γ-pyran-*5-t* (13, X = T). A 10-ml Carius tube was charged with 6 g (0.47 mol) of 3,3-dimethyl-δ-valerolactone, ~6 mL of tritium-rich water (60 mCi) and 0.5 g of triethylamine. The tube was sealed and stored for 20 h in a 105 °C oil bath. The tube was then opened and the brown solution extracted with ether, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Distillation (20 mm, 113–118 °C) gave 4 g of tritiated lactone. To these 4 g, 2.4 g of the protium analogue was added, and the 6.4-g mixture was then reduced and dehydrated, as described in the preparation of **4** above, to give 3.6 g of dihydropyran **13** (X = T): yield, 64%; cpm/mmol = 1.75×10^8. For reaction purposes a sample of this very "hot" dihydropyran was diluted by dissolving it in its protium analogue **4** to give a 3-g sample of dihydropyran **13** (X = T) with a count of ~6×10^6 cpm/mmol.

Preparation of Tritum-Rich 4,4-Dimethyl-2,3-dihydro-γ-pyran-*6-t* (14, X = T). 3,3-Dimethyl-δ-valerolactone (6.4 g) was treated as described for the preparation of **4** except that one-third the way through the reduction, a 7-mg sample of tritium-rich $LiAlH_4$ (5 mCi, New England Nuclear) was added through a side arm. The reaction was then worked up and the product dehydrated as described above in preparation of **4** to give 3.6 g (0.032 mol) of **14** (X = T): yield, 64%, cpm/mmol = 1×10^9. A sample of this very "hot" dihydropyran was diluted by dissolving it in its protium analogue **4** to yield a cpm/mmol of ~1.6×10^6.

Isolation of 22 and 23. **1** (250 μL) in 500 μL of solvent (acetonitrile or benzene) was irradiated until ~38 mL of oxygen was taken up. The samples were placed in corked test tubes containing several pellets of molecular sieves 4A and preparatively chromatographed on an 8 ft × ½ in. aluminum column packed with 20% Carbowax 20M on Chromosorb W AW DMCS 30/60 mesh. The injector and detector were set at 195 °C with a helium flow of 100 cc/min. Temperature programming conditions were as follows: (1) analysis began with oven temperature at 85 °C and it was held there for 18 min; (2) the temperature was then raised to 150 °C (~6 min) and held there for 14 min until **22** was eluted; (3) the temperature was then raised to 200 °C (~10–12 min) and held there until **23** came off. Approximate retention times for **22** and **23** under these conditions were 36 and 58 min, respectively. The NMR and IR spectra of **22** and **23** compared favorably with the spectra of the unmethylated analogues **27** and **28** obtained by Schaap.[19a] **22**: NMR (CCl_4) δ 1.15 (3 H, d), 1.3–2.6 (3 H, m), 4.40 (2 H, t), 8.00 (1 H, s), 9.60 (1 H, s); IR (CCl_4) 2992 (m), 2948 (m), 2824 (w), 2721 (w), 1739 (s), 1454 (m), 1432 (w), 1391 (w), 1370 (w), 1173 (s), 1035 (w), 923 (m), 820 (w) cm^{-1}. **23**: NMR (CCl_4) δ 2.00 (3 H, s), 2.38 (2 H, t), 4.35 (2 H, t), 5.70 (1 H, s); IR (CCl_4) 2870 (w), 1738 (s), 1455 (w), 1424 (w), 1411 (w), 1387 (w), 1370 (w), 1352 (w), 1300 (w), 1260 (m), 1215 (m), 1144 (m), 1086 (m), 1067 (m), 993 (w), 903 (w), 863 (w), 848 (w) cm^{-1}; mass spectrum, parent peak at *m/e* 112.

Preparation of 4-Formoxy-2-methylbutanal (22). **1** (600 μL) was ozonized in 5 mL of methylene chloride until the solution turned blue. The solution was then flushed with nitrogen until it turned colorless and ~1.6 g of triphenylphosphine was added. The solution was allowed to warm slowly to room temperature. The solvent of the resulting yellow solution was partially removed under reduced pressure and the remaining liquid bulb to bulb distilled under high vacuum. Final traces of solvent were then removed. VPC analysis showed only a single peak and the NMR and IR spectra were identical with those obtained in the previous section from photooxidation of **1**. The yield was ~80%.

By the same procedure 4-formoxybutanal **27** was also prepared.[19a]

2-Hydroxytetrahydrofuran (or 4-Hydroxybutanal) (30).[20,55] **27** (10 g, 0.08 mol) was stirred with 11.6 g (0.08 mol) of K_2CO_3 in 40 mL of dry methanol for 0.5 h. The slurry was filtered and the methanol was partially removed under reduced pressure. The remaining product was bulb to bulb distilled and last traces of methanol were removed to give the desired product in almost a 90% yield. **30** is an unusual organic compound in that it is soluble in water and not in ether: NMR ($CDCl_3$) δ 1.90 (4 H, m), 3.87 (2 H, m), 4.83 (br s, 1 H, hydroxylic), 5.52 (br s, 1 H) (no aldehydic absorptions were observed); mass spectrum, small parent peak at *m/e* of 88 with larger P − 1 at *m/e* of 87 and base peak at *m/e* of 71 (P − OH).

2-Hydroxy-3-methyltetrahydrofuran (or 4-Hydroxy-2-methylbutanal) (29). The procedure used was the same as described for the preparation of **30**, with **22** serving as the starting formate: NMR ($CDCl_3$) δ 1.08 (3 H, d), 1.6 (1 H, m), 2.1 (2 H, m), 3.92 (2 H, t), 4.90 (1 H, s), 5.17 (1 H, d); mass spectrum, small parent at *m/e* of 101 and base peak at *m/e* of 71 (P − CH_2OH).

Photooxidation Apparatus and Procedure. All photooxidations were carried out in the apparatus shown in Figure 1. Two 500-W projector lamps (Sylvania FBD, 120 V) were used as the light source and straw-colored filters were placed between the reaction flask and the lamps. The filters (Corning, CS 3-75), glass no. 3060) served to cut off all UV (transmission at 365 nm = 0.5%) and prevented premature bleaching of the dyes.

The gas buret, connected to the oxygenation cell, was alternately emptied and filled with oxygen three times; it was then isolated from the oxygenation cell while the cell was swept with oxygen for 10 min and stoppered with rubber septa. The reaction solution was introduced and oxygen passed over the system for 2 min. Cooling water and air for the cell and lamps were started and the gas buret was connected to the cell by a syringe needle through the septum. The system was allowed to equilibrate thermally for 10 min and an initial reading of the gas buret was then taken. With the magnetic stirrer operating at maximum speed, the solution was irradiated until ~16 mL of oxygen for **11** and **12**, and 13 mL for **13** and **14**, were absorbed (~50% completion). The lamps were then shut off, the system was again allowed to equilibrate for 10 min, and a final buret reading was taken. The reaction mixtures were then transferred to test tubes, serum capped, and stored in the refrigerator between VPC collections.

Isolation of Unreacted Starting Materials 11 and 12. Preparative vapor phase chromotography was performed directly on the reaction mixtures using a Model A-700 Aerograph Autoprep on a 10 ft × ¼ in. aluminum column packed with 20% Apiezon J on Chromosorb W AW DMCS 60/80 mesh. Temperature settings follow: oven, 72 °C; injector port, 138 °C; detector, 135 °C. With a sample size of ~300 μL and a flow of 58 mL of He gas/min, the retention times of the product were 15 min (peak width 8.5 min) for acetonitrile solutions and 17 min (peak width 6.0 min.) for benzene solutions. To prevent loss, injection port septa were changed after three injections.

Isolation of Unreacted Starting Materials 13 and 14. With the same apparatus, temperature settings were as follows: oven, 78 °C; injector port, 139 °C; detector, 139 °C. With a sample size of 350 μL and a flow of 70 mL/min of He gas, the retention times of the substrate were 17 min (peak width 10 min) for acetonitrile solutions and 21 min (peak width 8.5 min) for benzene solutions. Injection port septa were changed after two injections. Because of the high radioactivity of the samples only two VPC injections were required to give sufficient

sample for convenient counting.

Scintillation Counting. After two or three such 300-μL injections per sample, the product collected was injected into a serum capped scintillation vial[56] containing 4 mL of scintillation fluid.[57] The vial had been allowed to equilibriate for 1.5 h or more in the Mettler microbalance (Type M-5). The vial was handled with dry tweezers and weight readings to six decimal places were taken immediately before and after the injection; 6 mL more of scintillation fluid was then syringed into the vial. The vial was screw capped tightly and stored in the dark until counted. Each vial containing sample was wiped, dark adapted for ~½ h, and placed in the counting merry-go-round behind a tritium standard. The standard and samples were counted twice on each cycle to a 0.2% 2σ statistical counting error[29] (10^6 counts) and cycled between seven and nine times.[30] To assure the absence of any fortuitous scintillators or quenchers, each sample vial was also compared with an external standard. The counting was done in a Beckman LS-250 liquid scintillation system using a fixed-window-iso-set module (H^3-wide) preset to give 60% efficiency.

Isolation of Hydroperoxide 3. A solution of 200 μL of **1** in 1.6 mL of benzene/TPP was subjected to the standard photooxygenation procedure. Approximately one-half of the product mixture was subjected to high vacuum (>1 mm) bulb-to-bulb transfer for a period of 2 h at room temperature, leaving a residue of TPP and a colorless crystalline solid on the molecular sieves. This residue was then subjected to high vacuum bulb-to-bulb transfer at 50 °C, whereupon the colorless solid sublimed to a level above the heating bath and redeposited as colorless needles. This crystalline material (11 mg) was removed from the apparatus for VPC and NMR analysis: VPC analysis at 185 °C showed only one major peak with a retention time identical with that for **23**; NMR (CCl_4) δ* 1.82 (s), 2.2 (m), 3.8 (m), 5.3 (m), 9.8 (s).

2,2-Dimethyl-4-formoxybutanal (31). Formyl formate **31** can be obtained as the sole photooxidation product of **4** or from the ozonolysis of **4** by the procedure described for formyl formates **22** and **27** above: NMR (CCl_4) δ 1.11 (6 H, s), 1.88 and 4.17 (2 H, t, J = 7.0 Hz), 7.98 (s, 1 H), 9.46 (1 H, s).

Solvent Effects. Solvents used were commercially available high purity compounds and were taken from newly opened bottles. 4-Methyl-2,3-dihydro-γ-pyran (**1**, 50 μL) was dissolved in 600 μL of the desired solvent or solvent mixture and 10^{-3} M sensitizer. After preparing the apparatus (as described above), the samples were irradiated until ~7 mL of oxygen was taken up. The reaction mixtures were then immediately transferred to corked test tubes containing 12-25 1/6 in. type 4A molecular sieve pellets.

VPC analysis was performed directly on the reaction mixture using a 4 ft × ¼ in. aluminum column packed with 20% Carbowax 20M on 60/80 mesh Chromosorb P. An F & M Model 700 gas chromotograph (thermal conductivity detector) with the following conditions was used: helium flow, 100 mL/min; oven, 195 °C; detector, 240 °C; injector, 220 °C. Areas were determined by disk integration.

Product Isotope Effect Determination. 1 (50 μL) was dissolved in 400 μL of solvent containing 10^{-3} M sensitizer. The photooxygenation apparatus was prepared (as described above), and the solution was irradiated for a period of 1200 s for C_6H_6/TPP and 600 s in the case of acetonitrile/MB solutions. The reaction mixtures were then immediately serum capped and an injection made immediately onto the VPC column. Each run took ~28 min and during runs the samples were stored in the dark in the refrigerator.

VPC analysis was made using a Hewlett-Packard 7620A chromatograph (flame detector) with automatic digital integrator. The VPC column was a 10 ft × ¼ in. aluminum column packed with 20% Carbowax 20M on 30/60 mesh Chromosorb W AW DMCS. N_2 and H_2 flows were ~80 cc/min with an air flow of ~10 times the above. Thermal conditions were as follows: oven, 150 °C; injector, 210 °C; and flame, 270 °C. (Slope sensitivity: down and up, 1 mV/min; maximum noise suppression; base line reset delay, 0.5 min; peak, 1000; shoulder control, front-on, rear, 1000 mV; range, 10^4; recorder presentation, ×200 using 4-μL injections.)

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References and Notes

(1) (a) Address correspondence to the Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel. (b) Address correspondence to the Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129.
(2) For reviews, see ref 3–5.
(3) C. S. Foote, *Acc. Chem Res.*, **1**, 104 (1968).
(4) R. W. Denny and A. Nickon, *Org. React.*, **20**, 133 (1973).
(5) A. A. Frimer, Thesis, Harvard University, 1974.
(6) K. Gollnick, D. Halsch, and G. Schade, *J. Am. Chem. Soc.*, **94**, 1747 (1972).
(7) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970.
(8) W. E. Parham and H. F. Holmquist, *J. Am. Chem. Soc.*, **73**, 913 (1951).
(9) C. C. Price and J. A. Pappalardo, *J. Am. Chem. Soc.*, **72**, 2613 (1950).
(10) H. Rydon, *J. Chem. Soc.*, 594 (1936).
(11) G. Arth, *J. Am. Chem. Soc.*, **75**, 2413 (1953).
(12) In general, the first sequence is most convenient when one is interested in only some isotopic incorporation, as is the case for tritium labeling, where the label is followed by scintillation counting. The latter sequence is of the greatest utility when total exchange is desired, as is the case for deuterium labeling where the label is followed by NMR or mass spectroscopy. In such an instance if the base exchange is carried out ~6 times, the lactone will contain 94% deuterium at the α position and the final dihydropyran will have a 95% D content. In this research the deuterio analogues were often prepared in the exploratory stages of the syntheses.
(13) J. Bigeleisen, "Tritium in the Physical and Biological Sciences", Vol. 1, International Atomic Energy Agency, Vienna, 1962.
(14) C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **80**, 5585 (1958); see especially p 5585, eq 7. Although the equation is derived for primary isotope effects in which the stretching vibrations of the breaking or forming bonds are crucial, it should hold equally well for secondary isotope effects in which changes in the out-of-plane bonding frequency are important.[15,16] This is true since both vibrations follow Hooke's Law and isotope effects in both cases are due primarily to differences in zero point energies.[17]
(15) A. Steitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958).
(16) See review of E. Halevi in *Prog. Phys. Org. Chem.*, **1**, 109 (1963).
(17) Professors F. H. Westheimer and C. G. Swain, personal communications.
(18) See L. Melander, "Isotope Effects on Reaction Rates", Ronald Press, New York, N.Y., 1960, p 48 ff.
(19) (a) A. P. Schaap, Ph.D. Dissertation, Harvard University, 1970. (b) 5,6-Dihydro-2*H*-pyrone has recently been synthesized; see M. Nakagawa, M. Tonozuka, M. Obi, M. Kuichi, and T. Hino, *Synthesis*, 510 (1974).
(20) (a) A. C. Ott, M. F. Murray, and R. L. Pederson, *J. Am. Chem. Soc.*, **74**, 1239 (1952); see especially p 1240 in diagram. (b) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Haber, *ibid.*, **91**, 5675 (1969); see especially p 5676.
(21) This clearly rules out the possibility of solvent dependent Hock cleavage. See the question of G. O. Schenck in the discussion at the end of ref 28.
(22) K. Gollnick, *Adv. Photochem.*, **6**, 1 (1968).
(23) G. O. Schenck, *Angew. Chem.*, **64**, 12, 22 (1952).
(24) R. S. Atkinson, *Chem. Commun.*, 177 (1970); 585 (1971).
(25) R. S. Atkinson, *J. Chem. Soc., C*, 784 (1971).
(26) P. D. Bartlett, *Pure Appl. Chem.*, **27**, 597 (1971).
(27) P. D. Bartlett and A. P. Schaap, *J. Am. Chem. Soc.*, **92**, 3223 (1970).
(28) P. D. Bartlett, G. D. Mendenhall, and A. P. Schaap, *Ann. N.Y. Acad. Sci.*, **171**, 79 (1970).
(29) The 2σ statistical counting error (2/N where N is the total number of counts) is the 95% confidence level error. Hence, 10^6 counts yields a 2×10^{-3} or 0.2% error. Thus, for example, if the indicators display a count of 010204.5 cpm, 2.0%, the odds are 95% 20 to 1 that the true cpm rate is somewhere between 10 000 and 10 408 cpm.
(30) The scatter of the cpm values (i.e., discrepancy between the highest and lowest value) was not greater than 1.0%.
(31) See also a forthcoming paper by P. D. Bartlett and A. A. Frimer.
(32) (a) M. J. S. Dewar, *Chem. Br.*, **11** (3), 97 (March 1975); (b) M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **97**, 3978 (1975).
(33) E. A. Halevi, *Prog. Phys. Org. Chem.*, **1**, 109, 172 (1963).
(34) E. Koerner Von Gustorf, D. V. White, J. Leitich, and D. Hennebert, *Tetrahedron Lett.* 3113 (1969).
(35) J. Baldwin and J. Kapecki, *J. Am. Chem. Soc.*, **92**, 4874 (1970). These authors note that, for a two-step reaction via a radical or zwitterion, k_H/k_D should be ~1.0, and the normal value observed is thought to be a result of hyperconjugative interactions resulting from geometrical and/or orbital symmetry constraints. Alder, Baker, and Brown[36] however, argue that the normal value observed is more likely associated with the twisting of the sp^2 carbon out of conjugation with the neighboring p orbitals as required by a $[2_s + 2_a]$ cycloaddition. Presumably the difference in moments of inertia between an RCD and an RCH group makes an important contribution to the isotope effect.
(36) R. W. Alder, R. Baker, and J. M. Brown, "Mechanism in Organic Chemistry", Wiley, New York, N.Y., 1971, pp 260, 261.
(37) W. Weyler, Jr., L. R. Byrd, M. C. Caserio, and H. W. Moore, *J. Am. Chem. Soc.*, **94**, 1027 (1972).
(38) J. LeRoux and J. Basselier, *C. R. Hebd. Seances Acad. Sci.*, **271**, 461 (1970).
(39) J. C. Carmier and X. Deglise, *Bull. Soc. Chim. Fr.*, 868 (1973)).
(40) P. B. Merkel and D. R. Kearns, *J. Am. Chem. Soc.*, **94**, 7244 (1972).
(41) R. Huisgen and P. Otto, *J. Am. Chem. Soc.*, **90**, 5342 (1968).
(42) Similarly it has been concluded[41] from the stereospecificity of the cycloaddition of ketenes to enol ethers and from the relatively small solvent effect that this is a multicenter process with a polar transition state. For a review of cycloadditions with highly ionic intermediates, see ref 43.
(43) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **8**, 312 (1969).
(44) (a) F. A. Litt and A. Nickon, *Adv. Chem. Ser.*, **No. 77**, 118 (1968). (b) A. Nickon, V. T. Chuang, P. J. L. Daniels, R. W. Denny, J. B. DiGiorgio, J.

Tsunetsugu, H. G. Vilhuber, and E. Werstiuk, *J. Am. Chem. Soc.*, **94**, 5517 (1972). (c) A. Nickon, J. B. DiGirogio, and P. J. L. Daniels, *J. Org. Chem.*, **38**, 533 (1973). (d) The results cited by Nickon are per molecule and not per deuterium (personal communication).
(45) K. R. Kopecky, J. H. van de Sande, and C. Mumford, *Prepr., Div. Pet. Chem., Am. Chem. Soc.*, Abstr. No. 27 (Sept 1971).
(46) C. W. Jefford, M. H. Laffer, and A. F. Boschung, *J. Am. Chem. Soc.*, **94**, 8904 (1972).
(47) C. W. Jefford, A. F. Boschung, R. M. Moriarty, C. G. Rimbault, and M. H, Laffer, *Helv. Chim. Acta*, 2649 (1973).
(48) A. P. Schaap and G. R. Faler, *J. Am. Chem. Soc.*, **95**, 3381 (1973).
(49) (a) P. D. Bartlett, *Chem. Soc. Rev.*, 149 (1976); (b) C. W. Jefford and A. F. Boschung, *Tetrahedron Lett.*, 4771 (1976).
(50) W. Franke and R. Kraft, *Angew. Chem.*, **67**, 395 (1955).
(51) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 584.
(52) 9 ft × ¼ in. aluminum column packed with 20% Carbowax 20M on Chromosorb W AW DMCS: flow, 75 mL/min; injection temperature, 200 °C; detector temperature, 250 °C.
(53) G. F. Woods, Jr., "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1975, p 470.
(54) Y. R. Naves, P. Oschner, A. F. Thomas, and D. Lamparsky, *Bull. Soc. Chim. Fr.*, 1608 (1963).
(55) For alternate preparations of **30**, see (a) C. D. Hurd and W. H. Saunders, *J. Am. Chem. Soc.*, **74**, 5324 (1952); (b) W. J. Gensler and G. L. McLeod, *J. Org. Chem.*, **28**, 3194 (1963).
(56) Each scintillation vial used was washed initially with distilled water, dried in an oven, and capped.
(57) The scintillation fluid was prepared by dissolving in 1 gal of toluene 0.76 g of *p*-bis[2-(5-phenyloxazolyl)]benzene (POPOP) and 18.9 g of 2.5-diphenyloxazole (PPO). These scintillation grade compounds were obtained from New England Nuclear, Boston, Mass.

Photorearrangement of Azoxybenzene to 2-Hydroxyazobenzene. Evidence for Electrophilic Substitution by Oxygen

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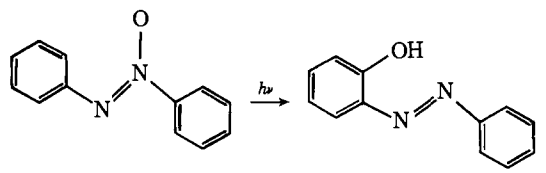
Abstract: The excited state responsible for the azoxybenzene photorearrangement is deduced to be $^1n,\pi^*$, not $^1\pi,\pi^*$ as assumed previously. INDO calculations indicate this state to be almost classical $^1n,\pi^*$, with excellent agreement between the calculated and observed spectrum being obtained. The theoretical model predicts an electrophilic role for oxygen during the rearrangement. Experiments with substituted azoxybenzenes support this model; among isomeric compounds having different substituents on the two rings, the higher quantum yield of reaction is observed when oxygen is to migrate into the ring bearing more electron-donating substituents. The evidence is permissive only, since it has not been possible to relate these quantum yields to relative rate constants for reaction.

Photolysis of azoxybenzene and its derivatives causes photomigration of the azoxy oxygen atom to the ortho position of the more distant aromatic nucleus[1] (eq 1). In this paper we



(1)

are concerned with (1) assignment of the reactive excited state and (2) correlation of the electron distribution in this excited state with the relative facility with which the photorearrangement takes place for simple substituted azoxybenzenes.

Assignment of Excited State. Tanikaga[2] noted that when azoxybenzene solutions are photolyzed together with benzophenone, the yield of the photorearrangement product drops and azobenzene is formed. He proposed that azobenzene emanates from the triplet state of azoxybenzene, and that photorearrangement is a reaction of the lowest observed singlet excited state (π,π^*). Monroe and Wamser demonstrated subsequently[3] that benzophenone acts in this reaction as a "chemical sensitizer" rather than as a source of triplet energy. Hence azobenzene is not a triplet state product at all, but the question of the state responsible for photorearrangement is unresolved.

We implicate a singlet excited state as the precursor of rearrangement on the following grounds. High-energy ketone sensitizers depress the photoefficiency owing to competing light absorption. The quantum yield for photorearrangement is unaffected by potential quenchers such as oxygen, piperylene, 1,3-cyclohexadiene, and pyrene. Heavy atom solvents, including 2-bromoethanol, methyl iodide, or xenon, do not affect the photoefficiency in ethanol.[4] Finally, in both benzene and ethanol, the quantum yield is unchanged over a wide temperature range, seeming to exclude a "hot" ground state intermediate.

What of the configuration of this excited state? The first observed absorption band of azoxybenzene in all solvents studied is associated with a π,π^* transition ($\nu_{max} \approx 31\,000$ cm^{-1}, $\epsilon \sim 14\,000$). To understand the nature of the low-lying excited states of azoxybenzene, we have undertaken a series of molecular orbital calculations, using an intermediate neglect of differential overlap technique described elsewhere.[6] After the ground state self-consistent field MOs were obtained, the 35 lowest energy π,π^* configurations were interacted to obtain the lowest lying π,π^* states. Likewise, interaction of 38 σ,π^* and π,σ^* configurations afforded the low-lying n,π^* states.

Input to the program included idealized crystallographic coordinates based on the structure of Krigbaum et al.[7a] for ethyl *p*-azoxybenzoate. Notable features of this crystallographic study are the long C–N bonds (1.56 Å vs. the usual R_{C-N} of 1.47 Å), the strong N–N bond of 1.155 Å (cf. $R_{N\equiv N}$ 1.10 Å and $R_{N=N}$ 1.24 Å), and the distortion from sp^2 hybridization at the N_2O bridge ($\angle NNO = 135°$). Additionally, the azoxy oxygen is located almost equidistant from the nearest carbon atom of each ring ($R = 2.67$ Å).

Calculated and observed transition energies and assignments are given in Table I. The spectral location of the first π,π^* band is confirmed, but the lowest singlet state is n,π^* at 26 000 cm^{-1}. Even after configuration interaction, this state is still