Electronic Effects in the Reaction of Propionaldehyde Oxide with Substituted Benzaldehydes[1]

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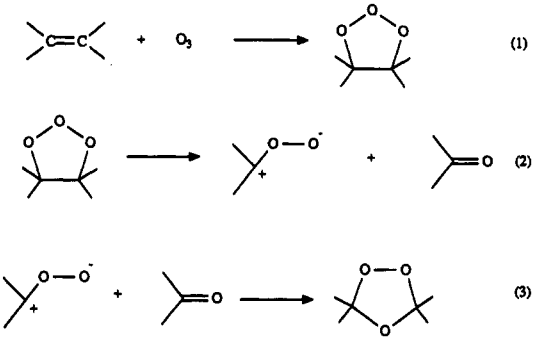
The relative rates of reaction of propionaldehyde oxide with para-substituted benzaldehydes have been measured and treated with the Hammett equation. The Hammett plot indicates that electron-withdrawing substituents in the benzaldehyde increase the reaction rate and give ρ = +0.25. Electron-donating substituents in the benzaldehyde also increase the rate (ρ = −0.85). The results are interpreted as indicating the presence of two related reaction pathways for ozonide formation. The cis/trans ratios of the ozonides produced in these reactions have been determined and also plotted against the Hammett σ constants. This plot indicates that electron-withdrawing substituents in the benzaldehyde increase the amount of cis ozonide formed in the reaction with propionaldehyde oxide. The results are interpreted in terms of current views of the mechanism of ozonolysis.

Introduction

While the first two steps of the overall scheme[2-4] for the ozonolysis reaction (Scheme I) have been studied[5-13] with the aid of linear free energy relationships, it is only recently that a similar approach has been taken for the third step. This delay was presumably due to the difficulty in isolating the kinetics in step 3 from the preceding steps. There are now two reports in the literature[14,15] in which linear free energy relationships have been used to study electronic effects in the reactions of carbonyl oxides with aldehydes (step 3, Scheme I). In the first of these Kuczkowski and co-workers[14] studied the reactions of substituted benzaldehyde oxides with similarly substituted benzaldehydes. The benzaldehyde oxides were produced by the ozonolysis of para-substituted styrenes and the necessary kinetic data were derived by applying a computer program to the yield data for the various ozonides produced in the ozonolysis. The relative rate coefficients were then treated with the Hammett relationship to give a ρ value of +1.4. While the ozonide-forming reaction has long been considered an example of a 1,3-dipolar addition reaction,[3,4] these data of Kuczkowski and co-workers appear to be the first experimental support for this view. We recently described[15] the reaction of benzophenone oxide with a series of substituted benzaldehydes. The benzophenone oxide was generated by the singlet oxygen oxidation of diphenyldiazomethane[16,17] and by the ozonolysis of tetraphenylethylene. In both cases plotting the relative rate data against Hammett substituent constants gave linear free energy relationships with ρ values of +0.48 and +0.76 for the singlet oxygen and ozonolysis methods, respectively. Thus our results confirmed the earlier observation of Kuczkowski[14] and indicate that the rate of ozonide formation in the systems studied is increased by electron-withdrawing groups in the aldehyde.

In all of these earlier studies of step 3, the carbonyl oxides used were substituted with aromatic groups only. In the work reported here we extend this approach to a carbonyl oxide containing an alkyl substituent. The carbonyl oxide, propionaldehyde oxide, was obtained by the

Scheme I



Scheme II

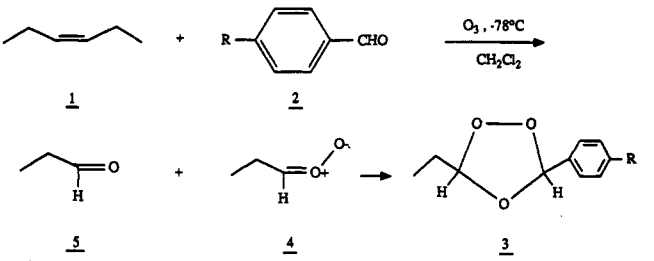


Table I. Yields of Ozonide 3 in the Ozonolysis of *cis*-3-Hexene in the Presence of 4-Substituted Benzaldehydes[a]

substit	σ value[b]	avg	no. of runs	std dev	RSD (%)	log
4-OMe	−0.36	0.7915	3	0.0351	4.44	−0.1015
4-*t*-Bu	−0.20	0.5880	3	0.0152	2.59	−0.2306
4-Et	−0.15	0.5426	4	0.0226	4.17	−0.2655
4-Me	−0.17	0.5198	4	0.0218	4.20	−0.2842
4-F	0.06	0.5982	4	0.0257	3.96	−0.2232
4-Cl	0.37	0.6591	3	0.0256	3.88	−0.1810
4-CF_3	0.54	0.8480	3	0.0056	0.66	−0.0716

[a] Yields of 3 (mmol) per mmol of O_3 consumed. [b] Taken from ref 19.

(1) Presented in part at the Midwest Regional Meeting of the American Chemical Society, Kansas City, MO, Nov 1986.
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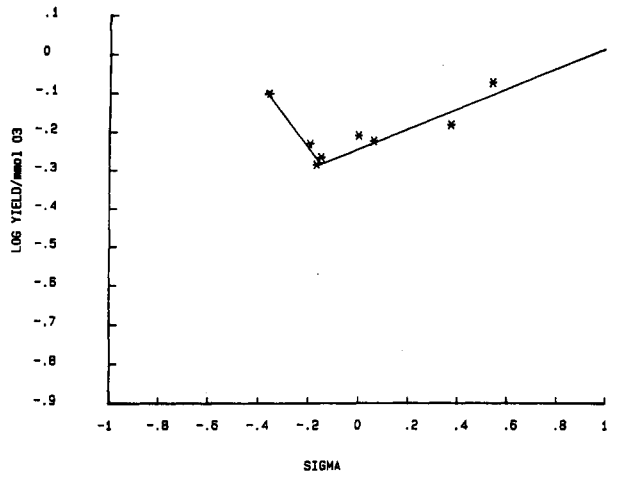


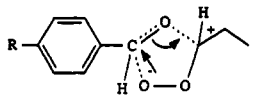
Figure 1. Plot of yields of ozonide 3 versus Hammett σ constants.

ozonolysis of *cis*-3-hexene under conditions where it would be encouraged to leave the solvent cage and to undergo the desired reaction with an added substituted benzaldehyde in competition with the otherwise-favored reaction with its cage reaction partner, propionaldehyde.

Results and Discussion

An equimolar solution of *cis*-3-hexene (1) and a 4-substituted benzaldehyde 2 in methylene chloride was ozonized at −78 °C (Scheme II). Ozonolysis was terminated after an expected 10% conversion of the olefin. The yields of the 3-ethyl-5-phenyl-1,2,4-trioxolanes 3 obtained were determined and are given in Table I. Ozonide yields were determined by using an NMR method and an internal integration standard as described earlier.[15] Methylene chloride was chosen for solvent because of its known tendency[18] to permit escape of the carbonyl oxide (e.g., 4) from the solvent cage. In this case the foreign aldehyde, i.e., the substituted benzaldehyde, competed very well with the parent aldehyde, propionaldehyde (5), to give the desired ozonide (Table I). In all cases ozonide 3 was the dominant product. Under the conditions of these experiments, that is, identical reaction conditions and low conversion, the yields may be taken as reflective of the relative rates of the reactions producing ozonides 3. The yield data were plotted against Hammett substituent constants (Figure 1).[19] When all of the data points are included, there appears, on first examination, to be a poor correlation with the substituent constants. The apparent scatter in the data points does not appear to be random however. Rather, the data fall into two categories depending on the manner in which the substituents in the benzaldehyde interact with the carbonyl reaction site. Further reflection suggests to us that we may be observing one of the classical deviations from linearity in Hammett plots. The data appear to fall into the "concave upward"[20] change of slope plot, which is indicative of the presence of two related reaction pathways. One of these intersecting lines consists largely of data for electron-withdrawing substituents and gives a $\rho = +0.248$ ($r = 0.944$) that is significant at the 99% confidence level when the goodness of fit analysis suggested by Chapman and Shorter[21] is applied. The second line is formed from the data for electron-donating substituents. This plot gives $\rho = -0.846$ ($r = 0.982$) with a statistical confidence level of 95%. It is noted that a related change of slope has been observed[22] in the first step (Scheme I) of the Criegee mechanism. In that case the change results from using aryl versus alkyl alkenes.

The observation that the yield data fall into two sets depending on whether the substituent in 2 is electron-withdrawing or electron-donating may provide a clue as to the identity of the mechanisms involved. In the case of the electron-withdrawing substituents the mechanism is the same as that observed in the two previous studies.[14,15] Ozonide formation is facilitated by the attraction of the negatively charged terminal oxygen in carbonyl oxide 4 to the carbonyl carbon in 2. This interaction leads to transition state 6 and generates a positive reaction constant.



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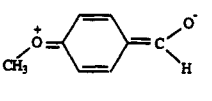

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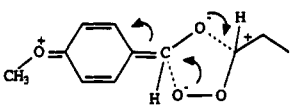

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This situation is to be contrasted with that in which the substituent in 2 is electron-donating. In this case the carbonyl group in the benzaldehyde will have a significant contribution from a resonance form, such as 7 in the methoxy-substituted aldehyde, in which much of the carbonyl character is lost. Similar forms may be written for the benzaldehydes containing 4-alkyl substituents through a combination of inductive or hyperconjugation effects. Approach of carbonyl oxide 4 is now likely to lead to a transition state, 8, in which bond formation between the positive charge in the carbonyl oxide and the carbonyl oxygen is more complete in a concerted, nonsynchronous cycloaddition. Alternatively this bond formation may initiate a nonconcerted cycloaddition. Operation of either of these possibilities might be expected to affect the rate of ozonide formation. If this formulation is correct, then one must also conclude that it favors ozonide formation, leading to what is otherwise an anomalously high yield in the methoxy-substituted compound, for example. Operation of either of these two possibilities for substituents with negative constants would lead to the observed second correlation with a negative reaction constant. The presence of these two reaction pathways, each with quite different electronic demands, would lead to the concave upward correlation shown in Figure 1.

This behavior of the benzaldehydes with electron-donating substituents is clearly different from that observed in the earlier studies in which the carbonyl oxide contained aryl substituents. It may be that in the aryl-substituted carbonyl oxides the positive charge is sufficiently delocalized into the aromatic system such that the attraction to the negative oxygen in the aldehyde (see 8) is attenuated.

All of the ozonides 3 produced in this work are new compounds. Spectroscopic data and elemental analyses are given in the Experimental Section. These ozonides also exist as cis and trans isomers. We have made stereo-

(18) Reference 3, Vol. I, p 89.
(19) The substituent constants used in this work were taken from McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420.
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(21) Chapman, N. B.; Shorter, J. *Correlation Analysis in Chemistry*; Plenum Press: New York, 1978; p 36.
(22) For a summary of these observations, see ref 4, p 220.

Table II. Cis–Trans Ratios in Ozonide 3

substit	σ value[b]	no. of runs	cis–trans ratio	std dev	RSD (%)
4-OMe	−0.36	4	0.97	0.0323	3.14
4-*t*-Bu	−0.20	4	0.69	0.0679	4.67
4-Et	−0.15	4	0.72	0.0603	4.32
4-Me	−0.17	4	0.65	0.0106	0.69
H	0.00	4	0.71	0.0643	4.58
4-F	0.06	3	0.72	0.0117	1.63
4-Cl	0.37	4	0.77	0.0112	0.87
4-CF_3	0.54	4	0.79	0.0572	4.50

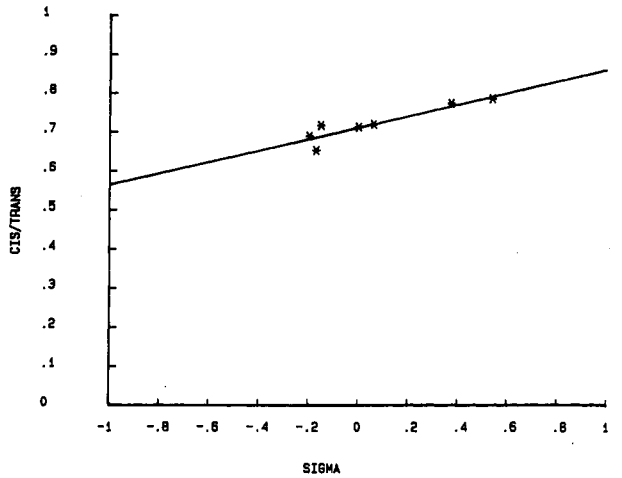

Figure 2. Plot of ozonide 3 cis/trans ratios versus Hammett σ constants.

chemical assignments following literature precedents. On the basis of combination of NMR, GPC, and TLC data, the cis configuration had been assigned to the isomer with the methine hydrogen at lower field in the NMR spectrum.[23] This assignment was consistent over a series of 3,5-dialkyl-substituted ozonides. On the other hand Criegee and Korber[24] had made assignments for the stilbene ozonides in which the trans isomer was assigned the lower field methine proton absorption. Later the use of a kinetic resolution of a trans *d,l* isomer[25] confirmed the earlier assignments for the dialkyl ozonides. Integration of the peaks for the methine protons in ozonides 3 revealed that the peak with the lower field δ value for the proton at the carbon bearing the ethyl substituent consistently corresponded to the peak with the higher field δ value for the proton at the aryl-substituted carbon. Stereochemical assignments in this series are thus consistent with both the assignments previously made[21] for the alkyl-substituted ozonides and those made by Criegee and Korber[24] for stilbene ozonides. Stereochemical distributions in ozonide 3 were determined as a function of the substituent in 2 (Table II).

A plot of the cis–trans distributions versus Hammett σ values is given in Figure 2. The point for the *p*-methoxy compound falls off the correlation line and is not shown. As described above, our interpretation of the Hammett rate plot (Figure 1) suggests that the *p*-methoxy compound is most likely to follow an alternative transition state to ozonide formation. The plot in Figure 2 reveals that the stereoisomer distribution falls in the range of approximately 0.64–0.77 with the trans isomer always dominant. What is most surprising about Figure 2 is that there is an apparent weak correlation between the stereoisomer distribution and the σ values, that is, the more electron-withdrawing substituents tend to give a higher amount of the cis isomer. To the best of our knowledge such a correlation has not been observed previously. Kuczkowski and Keul have described[26] the influence of the carbonyl partner on ozonide stereochemistry when the carbonyl is varied from ester to alkyl and then aryl aldehydes. In those cases the ozonide stereoselectivity was attributed to interactions between the carbonyl oxide and the carbonyl partner. In the current examples, the substituent would seem to be too far removed from the ozonide bond-making to exert a similar influence.

We believe that it may be possible to accommodate this apparent correlation with existing views on the factors involved in determining ozonide stereochemistry. The stereochemistry in ozonides 3 will be determined predominantly by the configuration of the carbonyl oxide produced in the ozonolysis of *cis*-3-hexene. According to the mechanism proposals made by Kuczkowski and co-workers[27] ozonolysis of 1 should lead to a preference for syn carbonyl oxide formation which, in turn, should lead to more trans ozonide 3 as found. Under the conditions of the current experiments the initially produced carbonyl oxide syn/anti distribution must be the same in all cases. Changes in ozonide stereoisomer distribution with change of substituent in the aldehyde partner must therefore be due to events occurring after the carbonyl oxides are formed. Comparison of Figures 1 and 2 indicates that the ozonides with electron-withdrawing substituents in the benzaldehyde are formed faster and also with a higher percent of cis ozonide. An explanation that accommodates this correlation is based on the asumption that isomerization could occur in the carbonyl oxide, which would alter the initially produced syn/anti ratio. While there are differing views[28] on the possibility of isomerization in the carbonyl oxide, we believe that some experimental observations, e.g., the influence of reaction warmup rate on ozonide stereochemistry,[30] are difficult to explain in the absence of such isomerization. Carbonyl oxide isomerization will tend to increase the amount of the more stable syn isomer[31] and hence the amount of trans ozonide. The ozonide-forming reactions that occur fastest will be more likely to intercept the initially formed carbonyl oxides, i.e., those that are less altered by equilibration and that have a higher anti content (though still favoring syn). This analysis predicts that the ozonides formed fastest, that is, those originating in aldehydes with the more electron-withdrawing groups, should give a higher cis ozonide content as observed.

A similar explanation can be used to understand the high cis content (c/t ca. 0.97) in the *p*-methoxy case (not shown in Figure 2). Here also the ozonide is formed much faster (Figure 1). The carbonyl oxide syn/anti distribution is close to that produced in the decomposition of the precursor 1,2,3-trioxolane. There has been little equilibration that would move the distribution to a higher syn carbonyl oxide content and thus increase the trans content in ozonides 3.

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(27) Lattimer, R. P.; Kuczkowski, R. L.; Gillies, C. W. *J. Am. Chem. Soc.* **1974**, *96*, 348.
(28) For example, Kuczkowski concludes[26] that no equilibration occurs in HDCOO, but invokes[29] equilibration in CH_3CHOO.
(29) Choe, J. I.; Srinivasan, M.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 4703.
(30) Reference 3, Vol. 1, p 100.
(31) Reference 3, Vol. II, p 377.

Experimental Section

Materials. Deuteriochloroform was purchased from Aldrich Chemical Co., Milwaukee, WI. Other solvents were obtained from Fischer Scientific Co., Fairlawn, NJ. Tetrachloromethane and dichloromethane were purified by distillation under nitrogen over calcium hydride and were stored over molecular sieves. *cis*-3-Hexene was purchased from Wiley Organics, Columbus, OH. 4-tert-Butylbenzaldehyde was purchased from Lancaster Synthesis Limited, Windham, NH. Benzaldehyde, 4-methoxybenzaldehyde, 4-methylbenzaldehyde, 4-ethylbenzaldehyde, 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, and 4-(trifluoromethyl)benzaldehyde were obtained from Aldrich Chemical Co., Milwaukee, WI.

Chromotography Supplies. Preparative TLC glass plates (20 × 20 cm) precoated with 1-mm silica gel with fluorescent indicator (254 nm) were purchased from Analtech Inc., Newark, DE. Analytical TLC plates precoated with 0.1-mm silica gel with fluorescent indicator (254 nm) were purchased from Eastman Kodak Co., Rochester, NY. Alumina (activity 1) (80–200 mesh) and silica gel (80–100 mesh) for column chromatography were purchased from Fischer Scientific, Fairlawn, NJ.

Instrumentation. Infrared spectra for solid ozonides were obtained in KBr pellets. Infrared spectra for liquid ozonides were obtained from neat samples in thin films with 1-mm AgCl plates. Melting points were measured on a capillary melting point apparatus and are uncorrected. Ozone was produced in a commercial ozone generator. NMR spectra were measured on a 60- or 300-MHz NMR spectrometer using CCl_4 or deuteriochloroform, respectively, as solvents.

Preparation of 2-Phenyl-1,3-dioxolane. The published[15] procedure was followed. The 2-phenyl-1,3-dioxolane was separated by fractional distillation at reduced pressure, bp 130 °C (16 mm).

General Ozonolysis Procedure. Ozone was produced in a commercial ozone generator and delivered at a rate of 0.17 to 0.22 mmol/min. The reaction vessel consisted of a Pyrex-brand impinger equipped with a Dewar condenser. Exhaust gases were passed through a 5% KI solution in gas washing bottles. The ozone rate was determined just prior to each reaction set by passing the ozone stream through a 5% solution of KI for 5 min followed by iodometric titration. The amount of ozone consumed in each reaction was determined by titrating the KI solution in series with the reaction and subtracting the corresponding amount of ozone from that delivered to the reaction vessel.

Ozonolysis of *cis*-3-Hexene in the Presence of a Substituted Benzaldehyde. A solution of 5 mmol (0.425 g) of *cis*-3-hexene and 5 mmol of the freshly distilled aldehyde in 10 mL of dichloromethane was placed in a 50-mL Pyrex-brand impinger and cooled for 30 min at −18 °C. The reaction vessel was then cooled to −78 °C in a dry ice–acetone bath and sparged with helium for 5 min. Ozone (0.5 mmol) was passed through the solution followed by a 5-min helium sparge. The reaction mixture was allowed to warm to −18 °C for 30 min prior to solvent removal. At the conclusion of each reaction the solvent was removed by rotary evaporation and an aliquot (0..0113 g, 0.075 mmol) of the internal standard, 2-phenyl-1,3-dioxolane, was accurately weighed and added to the crude reaction mixture. The mixture was then dissolved in 4 mL of deuteriochloroform. The NMR spectra of the reaction mixtures were then determined at 300 MHz and the yields of ozonides obtained by integrating the region containing the methine protons of the ozonides and the internal standard. A minimum of three runs was made for each aldehyde. The yields are given in Table I. The ratios of the cis and trans isomers of the ozonides were determined by comparing the integrations of the methine proton peaks and are given in Table II.

Isolation and Analysis of Substituted Ozonides. The solvent was removed from each crude reaction mixture by rotary evaporation. The crude reaction mixtures were separated initially by flash column chromatography with 80–100-mesh silica gel and 95:5 pentane/ethyl ether. The fraction containing the ozonide and other peroxides was further separated by preparative TLC on glass plates coated with 1.0 mm of silica gel. The samples were applied to the plates by dissolving them in CH_2Cl_2 and spotting in a continuous line 1–1.5 cm from the bottom of the plate with a capillary tube. The plates were developed with 90:10 pentane/ethyl ether and air dried. The ozonides were located by using UV light and were removed from the plates. The silica gel portions containing the ozonides were extracted twice with CH_2Cl_2. The solvent was removed by rotary evaporation. Residual solvent was removed by treating the samples to high vacuum for 16 h.

Test of Acid Sensitivity of the Reaction Mixtures. The following procedure was carried out in order to determine whether the ozonide mixtures were altered by the presence of any acid that may have been produced during the ozonolyses. A crude reaction mixture, using benzaldehyde as the aldehyde, was prepared following the procedure for the *cis*-3-hexene ozonolyses described above. A 2-mL aliquot of a 0.001 M solution of benzoic acid in CH_2Cl_2 was added to the crude reaction mixture. The solvent was stripped by rotary evaporation and a 0.10-g aliquot of 2-phenyl-1,3-dioxolane was added to the crude mixture. The resulting mixture was dissolved in 5 mL of deuteriochloroform and stored at −18 °C. The NMR spectrum of the sample was taken after 3 h and after 30 h of storage. No decrease in the ratio between the methine proton of the internal standard and the methine protons of the ozonide was observed.

Ozonide Physical Data. 3-Ethyl-5-phenyl-1,2,4-trioxolane (cis + trans isomers): IR (AgCl) 3080, 3060, 2990, 2900, 1700, 1600, 1580, 1500, 1460, 1380, 1310, 1290, 1220, 1180, 1120, 1090, 1050, 1020, 1000, 930, 910, 890, 860, 760, 740, 720, 700, 670, 640, 520, 490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.58 (m, 5 H), 6.11, 6.05 (s, 1 H), 5.47, 5.40 (t, J = 9 Hz, 1 H), 1.82–1.92 (m, 2 H), 1.01–1.15 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 133.80, 132.56, 130.59, 130.23, 128.66, 128.52, 127.83, 127.39, 106.17, 103.98, 103.43, 25.92, 24.14. Anal ($C_{10}H_{12}O_3$) C, H.

3-Ethyl-5-(4-methoxyphenyl)-1,2,4-trioxolane (cis + trans isomers): IR (AgCl) 2980, 2920, 2815, 1600, 1580, 1490, 1460, 1435, 1360, 1285, 1265, 1190, 1170, 1155, 1040, 875, 780, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95–7.35 (m, 4 H), 6.10, 6.05 (s, 1 H), 5.47, 5.38 (t, J = 9 Hz, 1 H), 3.79 (s, 1 H), 1.82–1.95 (m, 2 H), 1.05–1.15 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.85, 159.77, 135.86, 134.22, 129.74, 129.66, 120.10, 119.64, 116.32, 115.75, 112.83, 112.59, 106.29, 106.04, 103.77, 103.17, 55.19, 55.15, 25.79, 24.14, 8.23, 7.75. Anal ($C_{11}H_{14}O_4$) C, H.

3-Ethyl-5-(4-*tert*-butylphenyl)-1,2,4-trioxolane (cis + trans isomers): IR (AgCl) 3060, 2080, 1610, 1510, 1490, 1450, 1420, 1380, 1360, 1320, 1260, 1210, 1190, 1180, 1110, 1050, 1020, 960, 930, 910, 830, 790, 760, 700, 640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.63 (m, 4 H), 6.16, 6.13 (s, 1 H), 5.43, 5.48 (t, J = 9 Hz, 1 H), 1.90–2.0 (m, 2 H), 1.42 (s, 9 H), 1.07–1.16 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 153.5, 153.1, 130.72, 129.56, 127.44, 127.08, 125.38, 125.3, 106.01, 105.85, 104.74, 104.68, 103.76, 103.26, 34.59, 26.01, 25.4, 23.97, 8.06, 7.63, 7.57. Anal ($C_{14}H_{20}O_3$) C, H.

3-Ethyl-5-(4-ethylphenyl)-1,2,4-trioxolane (cis + trans isomers): IR (AgCl) 2960, 2940, 2740, 1920, 1700, 1610, 1580, 1520, 1460, 1380, 1310, 1270, 1220, 1170, 1120, 1080, 1020, 830, 740, 700, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.52 (m, 4 H), 6.10, 6.07 (s, 1 H), 5.50, 5.42 (t, J = 9 Hz, 1 H), 2.72 (q, J = 18 Hz, 2 H), 1.82–1.97 (m, 5 H), 1.28 (t, J = 12 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.97, 131.04, 128.17, 127.91, 106.28, 105, 104.07, 28.81, 26.20, 24.17, 15.50, 8.25, 7.98. Anal ($C_{12}H_{16}O_3$) C, H.

3-Ethyl-5-(4-methylphenyl)-1,2,4-trioxolane (cis + trans isomers): IR (AgCl) 2980, 2910, 2890, 1910, 1800, 1700, 1620, 1510, 1460, 1380, 1360, 1310, 1220, 1210, 1180, 1110, 1080, 1050, 1020, 1000, 940, 920, 880, 860, 810, 780, 750, 730, 680, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.52 (m, 4 H), 6.10, 6.07 (s, 1 H), 5.50, 5.43 (t, J = 9 Hz, 1 H), 2.39 (s, 3 H), 1.86–1.97 (m, 2 H), 1.00–1.17 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.65, 140.25, 129.34, 129.27, 127.84, 127.46, 106.29, 106.11, 105.01, 104.96, 104.07, 103.55, 26.20, 25.60, 24.18, 24.05, 21.36, 21.33, 8.25, 7.98, 7.77. Anal ($C_{11}H_{14}O_3$) C, H.

3-Ethyl-5-(4-fluorophenyl)-1,2,4-trioxolane (cis and trans isomers): IR (AgCl) 2980, 2920, 1610, 1510, 1465, 1370, 1290, 1230, 1150, 1110, 1045, 1010, 830, 790, 730, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07–7.52 (m, 4 H), 6.09, 6.03 (s, 1 H), 5.45, 5.38 (t, J = 9 Hz, 1 H), 1.82–1.92 (m, 2 H), 1.02–1.11 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.90, 162.80, 161.15, 161.0, 129.80, 129.30, 115.80, 115.40, 106.0, 105.90, 103.8, 102.6, 27.7, 23.9, 7.8, 5.2. Anal ($C_{10}H_{11}O_3F$) C, H, F.

3-Ethyl-5-(4-chlorophenyl)-1,2,4-trioxolane (cis + trans isomers): IR (AgCl) 2990, 1910, 1730, 1700, 1600, 1490, 1470, 1420, 1370, 1300, 1280, 1260, 1210, 1180, 1090, 1050, 1020, 940,

920, 820, 730, 700, 680, 620, 470 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.48 (m, 4 H), 6.08, 6.00 (s, 1 H), 5.42, 5.35 (t, J = 9 Hz, 1 H), 1.82–1.92 (m, 2 H), 1.00–1.11 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 129.15, 128.93, 128.71, 128.64, 106.45, 106.18, 103.16, 102.57, 25.54, 24.12, 8.25, 7.76. Anal ($C_{10}H_{11}O_3Cl$) C, H, Cl.

3-Ethyl-5-[4-(trifluoromethyl)phenyl]-1,2,4-trioxolane (cis + trans isomers): IR (AgCl) 2990, 2900, 1925, 1620, 1520, 1460, 1420, 1320, 1210, 1160, 1120, 1070, 1020, 920, 880, 830, 760, 720, 680, 650, 640, 600, 430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.68 (m, 4 H), 6.17, 6.07 (s, 1 H), 5.43, 5.34 (t, J = 9 Hz, 1 H), 1.79–1.92 (m, 2 H), 0.98–1.07 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 128.04, 127.41, 125.61, 125.56, 125.51, 106.50, 106.18, 102.76, 25.01, 24.12, 7.71. Anal ($C_{11}H_{11}O_3F_3$) C, H, F.

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Registry No. Propionaldehyde oxide, 627-39-4; 4-methoxybenzaldehyde, 123-11-5; 4-*tert*-butylbenzaldehyde, 939-97-9; 4-ethylbenzaldehyde, 4748-78-1; 4-methylbenzaldehyde, 104-87-0; 4-fluorobenzaldehyde, 459-57-4; 4-chlorobenzaldehyde, 104-88-1; 4-(trifluoromethyl)benzaldehyde, 455-19-6; *cis*-3-hexene, 7642-09-3; *cis*-3-ethyl-5-phenyl-1,2,4-trioxolane, 135658-31-0; *trans*-3-ethyl-5-phenyl-1,2,4-trioxolane, 135638-98-1; *cis*-3-ethyl-5-(4-methoxyphenyl)-1,2,4-trioxolane, 135638-99-2; *trans*-3-ethyl-5-(4-methoxyphenyl)-1,2,4-trioxolane, 135639-00-8; *cis*-3-ethyl-5-(4-*tert*-butylphenyl)-1,2,4-trioxolane, 135639-01-9; *trans*-3-ethyl-5-(4-*tert*-butylphenyl)-1,2,4-trioxolane, 135658-32-1; *cis*-3-ethyl-5-(4-ethylphenyl)-1,2,4-trioxolane, 135639-02-0; *trans*-3-ethyl-5-(4-ethylphenyl)-1,2,4-trioxolane, 135639-03-1; *cis*-3-ethyl-5-(4-methylphenyl)-1,2,4-trioxolane, 135639-04-2; *trans*-3-ethyl-5-(4-methylphenyl)-1,2,4-trioxolane, 135639-05-3; *cis*-3-ethyl-5-(4-fluorophenyl)-1,2,4-trioxolane, 135639-06-4; *trans*-3-ethyl-5-(4-fluorophenyl)-1,2,4-trioxolane, 135639-07-5; *cis*-3-ethyl-5-(4-chlorophenyl)-1,2,4-trioxolane, 135639-08-6; *trans*-3-ethyl-5-(4-chlorophenyl)-1,2,4-trioxolane, 135639-09-7; *cis*-3-ethyl-5-[4-(trifluoromethyl)phenyl]-1,2,4-trioxolane, 135639-10-0; *trans*-3-ethyl-5-[4-(trifluoromethyl)phenyl]-1,2,4-trioxolane, 135639-11-1.

Anomeric-like Substituent Effects on the Chair–Chair Conformational Equilibrium of the 2-Oxo-1,3,2-oxazaphosphorinane Ring System[1]

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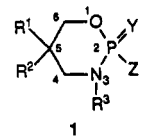
The chair–chair equilibria for a series of 5,5-dimethyl-2-oxo-(2-*p*-X-anilino)-1,3,2-oxazaphosphorinanes were determined by ^{1}H NMR. The percentage of chair conformer with the *p*-X-anilino group axial is increased by the presence of electron withdrawing X, while the opposite is true for electron-donor para X. Reasonably good linear plots of log K vs σ_p were obtained in the solvents acetone-d_6, CD_3CN, and CD_3NO_2 with ρ = 0.28–0.36. These results are interpreted in terms of the dominance of the endo anomeric effect involving overlap of the endocyclic N(3) and O(1) p lone pairs with the axial P–N σ^* orbital (*p*-XC_6H_4NHP).

1,3,2-Oxazaphosphorinanes **1** can be viewed as cyclohexanes in which carbon atoms have been replaced by oxygen, phosphorus, and nitrogen atoms. The effects on the conformational properties of cyclohexane of making such substitutions are of basic interest. These ring systems take on further significance since they are an integral structural part of the clinically valuable antitumor agent cyclophosphamide **2** and its congeners.[2] A thorough



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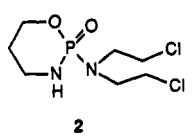

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knowledge of the conformational properties of the 1,3,2-oxazaphosphorinane ring system should be beneficial to a detailed understanding of the effects of conformation on the oxidative metabolic activation of cyclophosphamide, the transport properties of the metabolites, and their breakdown to cytotoxic products.

In previous work,[3] it was shown that chair–chair and chair–twist equilibria are strongly influenced by the following (see structure **1**): (1) the size of substituent R^3 and (2) the steric and electronic properties of Z. The chair-to-twist free energy change was found to be remarkably

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