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AND THEIR EPOXIDE METABOLITES

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INTRODUCTION

The chlorinated ethylenes, with which this paper deals, are examples of halogenated hydrocarbons, a large class of compounds that have received considerable publicity in recent years. This has come about because, first, they are widely released into the environment, and, second, certain of them have been shown to be carcinogenic. The widespread distribution of halogenated hydrocarbons results from the fact that some of them are produced and used industrially on a very large scale; consequently, exposure to them, on the part of the general population as well as of industrial workers, is often of a chronic nature. This means that effects that might be insignificant on an occasional basis have the opportunity to accumulate.

Of course, not all halogenated hydrocarbons are carcinogens; many are not even mutagens. In view of the important economic and social role of these compounds, there is a great need for determining, for as many as possible, their carcinogenic potencies and the degrees of hazard associated with them. A considerable amount of experimental work is in progress in many laboratories, seeking to provide answers to these questions. The task is a formidable one, involving lengthy and difficult animal studies, and, unfortunately, the results are usually not absolute, but rather depend on a number of very specific factors, such as the species and even the strain of the animal, its age and sex, and the concentration, duration, and mode of administration of the compound. For instance, vinyl chloride produces Zymbal gland carcinomas in Sprague-Dawley male rats but not in Wistar rats; it causes liver tumors in one-day-old Sprague-Dawley rats but not in those that have reached the age of thirteen weeks.¹

It is also essential to develop greater insight into the structural and electronic factors that govern the behavior of the halogenated hydrocarbons. This would permit the growing body of experimental data to be fitted into some sort of a conceptual framework, and would make it possible to better understand and predict the biological activities of these compounds. The present study is a step in this direction.

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THE CHLORINATED ETHYLENES

General Background

In this paper, we report the initial results of an investigation of the chlorinated ethylenes. These six molecules, listed in TABLE 1,† are well suited for our purposes because they have nearly identical structures, differing only in the number and location of chlorine atoms, and yet exhibit a range of biological behavior. It may, therefore, be possible to establish a relationship between the one distinguishing structural feature and their various activities.

TABLE 1
THE CHLORINATED ETHYLENES

Name	Structural Formula
Ethylene	$\begin{array}{c} \text{H} & & \text{H} \\ & \diagdown & / \\ & \text{C} = \text{C} \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array}$
Vinyl chloride (1-Chloroethylene)	$\begin{array}{c} \text{Cl} & & \text{H} \\ & \diagdown & / \\ & \text{C}_1 = \text{C}_2 \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array}$
Vinylidene chloride (1,1-Dichloroethylene)	$\begin{array}{c} \text{Cl} & & \text{H} \\ & \diagdown & / \\ & \text{C}_1 = \text{C}_2 \\ & / & \diagdown \\ \text{Cl} & & \text{H} \end{array}$
cis-1,2-Dichloroethylene	$\begin{array}{c} \text{Cl} & & \text{Cl} \\ & \diagdown & / \\ & \text{C} = \text{C} \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array}$
trans-1,2-Dichloroethylene	$\begin{array}{c} \text{Cl} & & \text{H} \\ & \diagdown & / \\ & \text{C} = \text{C} \\ & / & \diagdown \\ \text{H} & & \text{Cl} \end{array}$
Trichloroethylene	$\begin{array}{c} \text{Cl} & & \text{Cl} \\ & \diagdown & / \\ & \text{C}_1 = \text{C}_2 \\ & / & \diagdown \\ \text{Cl} & & \text{H} \end{array}$
Tetrachloroethylene (Perchloroethylene)	$\begin{array}{c} \text{Cl} & & \text{Cl} \\ & \diagdown & / \\ & \text{C} = \text{C} \\ & / & \diagdown \\ \text{Cl} & & \text{Cl} \end{array}$

The chlorinated ethylenes are also of particular interest because of their industrial importance. For example, the total 1979 production of vinyl chloride in the United States was 7.54 billion pounds, which gave it nineteenth ranking among the chemicals produced in the greatest quantities.² Vinylidene chloride, trichloroethylene, and tetrachloroethylene also find extensive commercial use.

†TABLE 1 also includes ethylene. It is a logical reference point for investigations of the effects of chlorine substitution, and will be so used throughout this paper.

TABLE 2
MUTAGENIC AND CARCINOGENIC ACTIVITIES OF THE CHLORINATED ETHYLENES

Molecule	Formula	Mutagenic and Carcinogenic Activities
Ethylene	$\text{CH}_2=\text{CH}_2$	mutagenicity and carcinogenicity uncertain ^{1,2,3}
Vinyl chloride	$\text{CHCl}=\text{CH}_2$	definitely established to be both mutagenic ² and carcinogenic ^{1,2,3,4}
Vinylidene chloride	$\text{CCl}_2=\text{CH}_2$	weakly mutagenic; ^{1,2,3,4} very weakly carcinogenic ^{1,2,4}
cis-1,2-Dichloroethylene	$\text{CHCl}=\text{CHCl}$	possibly mutagenic; ¹ apparently not carcinogenic ^{1,2}
trans-1,2-Dichloroethylene	$\text{CHCl}=\text{CHCl}$	not mutagenic; ² apparently not carcinogenic ^{1,2}
Trichloroethylene	$\text{CCl}_2=\text{CHCl}$	weakly mutagenic; ^{1,2,3,4} weakly carcinogenic ^{1,2,3,4}
Tetrachloroethylene	$\text{CCl}_2=\text{CCl}_2$	not mutagenic; ^{1,2,3,4} weakly carcinogenic ^{2,4}

Biological Properties

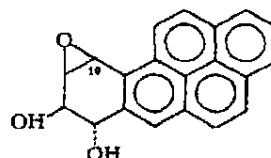
In TABLE 2, we summarize the currently-available data concerning the mutagenic and carcinogenic activities of the chlorinated ethylenes. These data are based on animal, bacterial, and cell culture studies. (The earlier comments concerning the extreme sensitivity of the results of such studies to a variety of factors, and the difficulty that is often encountered in trying to reach a definite conclusion, should be kept in mind.) The table shows the carcinogenic activities to range from that of vinyl chloride, which is the strongest and best-established carcinogen among these compounds, to the apparent inactivities of the *cis*- and *trans*-1,2-dichloroethylenes.

It is generally accepted that the initial metabolic step undergone by the chlorinated ethylenes is epoxidation of the double bond.⁵⁻⁷ To whatever extent each of these compounds is carcinogenic, it is believed to be this metabolically-produced epoxide, such as the following structure (1) in the case of vinyl chloride, that is the active form, the "ultimate carcinogen."



This is somewhat reminiscent of the situation with the polynuclear aromatic hydrocarbons. It has now been established that the metabolically-formed diol epoxide (2) is a carcinogenically-active form of benzo[a]pyrene, and that analo-

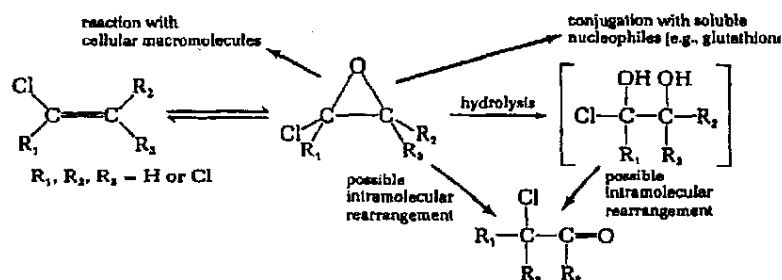
gous metabolites apparently play the same role for at least some other polynuclear aromatic hydrocarbons.⁷⁻¹¹ This diol epoxide of benzo[a]pyrene has been shown to react with nucleophilic sites on DNA and other cellular macromolecules via an opening of the C₁₀-O bond of the epoxide ring and subsequent binding at C₁₀.⁷⁻¹¹ It is believed that an interaction of this sort is the key to the carcinogenicity of the diol epoxide.



(2)

Similarly, it has been demonstrated that vinyl chloride and trichloroethylene can bind to cellular macromolecules, including DNA, and it is believed to be their metabolically-produced epoxides that are actually involved in this.¹²⁻¹⁶ Such interactions are, presumably, key steps in the carcinogenic mechanisms.

Of course, the epoxides can also follow other, nontoxic metabolic pathways, as shown in the following generalized scheme:¹²⁻¹⁶



It may well be that the activities of some of these compounds as carcinogens depend largely upon the balance, in each case, between these various competing reactions.

The preceding discussion of initial metabolic activation to epoxides, which act as ultimate carcinogenic forms of some chlorinated ethylenes, should be qualified by mentioning that this is reasonably well established only for vinyl chloride. Absorption spectra, trapping experiments, and enzyme activation studies all point to the critical role played by its epoxide.^{12-16,19} For the other compounds, the situation is less clear-cut. For example, Bartsch and his collaborators have been unsuccessful in attempts to trap the epoxide of either vinylidene chloride or trichloroethylene.¹⁹ Nevertheless, on the basis of other evidence, such as the effects of modifiers of hepatic mono-oxygenase activity (this is the enzyme that catalyzes epoxide formation), it is widely believed that the other carcinogenic

chlorinated ethylenes follow the same general toxic metabolic route as vinyl chloride.¹⁸⁻²¹

In view of the apparently key function of the epoxides in the carcinogenic process, it is essential to know more about their properties, such as structures, stabilities, reactivities, ease of ring opening, and charge distributions. Unfortunately, relatively little information of this kind is presently available. All the epoxides have been synthesized except that of vinylidene chloride.^{22,23} Hydrolysis studies have been carried out under physiological conditions for the epoxides of vinyl chloride, trichloroethylene, and tetrachloroethylene, as well as for ethylene oxide.²⁴ Taking the latter as a reference point, the presence of chlorine was found to considerably increase the hydrolytic reactivity; the rate constants for the chlorinated epoxides were larger by factors of 10^3 - 10^4 . Both in these hydrolysis investigations and also in thermolysis studies, the available evidence was taken to indicate that it was the C—O bond involving the less substituted carbon that was broken.^{21,25}

One of our primary aims in this work is to learn more about the properties of the chlorinated ethylene epoxides. An important goal is to relate these properties to the biological activities of the compounds, and also to the numbers and locations of the chlorine atoms. This would provide some insight into the manner in which the presence of the chlorines affects the biological behaviors of the compounds. Our approach is a computational one, as will be described in the next section.

METHOD

We have calculated the properties of the chlorinated ethylenes and their epoxides by means of *ab initio* self-consistent-field molecular orbital wavefunctions using the Gaussian 70 procedure with an STO-5G basis set.²⁶ Our first step was to compute optimized structures for both groups of molecules. For the chlorinated ethylenes, a considerable amount of experimentally-determined structural information is available, but this is not so for their epoxides. Accordingly, optimized geometries were computed for both the parent molecules and their epoxides in order to permit meaningful comparisons and assessments of the effects of epoxidation.

RESULTS AND DISCUSSION

Structures

The calculated structures of the chlorinated ethylenes (and ethylene itself) are given in TABLE 3. In general, they are in good agreement with the experimentally-measured structural parameters, the main difference being that the computed C—Cl bond lengths are 0.03-0.04 Å longer than the observed values. All the molecules are planar.

The calculated structures for the epoxides are in TABLE 4. Experimental data is available only for ethylene oxide, and they agree well with the computed results. The epoxides are, of course, nonplanar.

TABLE 3
 CALCULATED PROPERTIES OF CHLORINATED ETHYLENES*†

Molecule	Structure		Dipole Moment‡	Atomic Charges
	Distances	Angles		
Ethylene	C—C: 1.31 (1.332 – 1.339) C—H: 1.08 (1.084 – 1.086)	H—C—H: 116 (115.5 – 117.6)	$\mu_x = 0$ $\mu_y = 0$ $\mu_{tot} = 0$	C: -0.13 H: +0.07
Vinyl chloride§	C—C: 1.31 (1.32 – 1.33) C—H: 1.08 (1.08) C—Cl: 1.77 (1.72 – 1.740)	Cl—C—C: 123 (119.5 – 125) H—C—Cl: 112 (114) H—C—H: 116 (119) H—C ₂ —C ₁ : 122 (121)	$\mu_x = 1.379$ $\mu_y = 1.739$ $\mu_{tot} = 2.219$	C ₁ : -0.01 C ₂ : -0.12 Cl: -0.15 H(C ₁): +0.10 H: +0.09
Vinylidene chloride§	C—C: 1.31 (1.324 – 1.325) C—H: 1.08 C—Cl: 1.77 (1.707 – 1.727)	Cl—C—Cl: 115 (113.6 – 122.7) H—C—H: 118	$\mu_x = 2.340$ $\mu_y = 0$ $\mu_{tot} = 2.340$	C ₁ : +0.08 C ₂ : -0.11 Cl: -0.09 H: +0.11
cis-1,2-Dichloroethylene	C—C: 1.31 (1.336) C—H: 1.08 C—Cl: 1.76 (1.722)	Cl—C—C: 125 (123) H—C—C: 121	$\mu_x = 0$ $\mu_y = 3.020$ $\mu_{tot} = 3.020$	C: -0.02 Cl: -0.10 H: +0.12
trans-1,2-Dichloroethylene	C—C: 1.31 (1.343) C—H: 1.08 C—Cl: 1.77 (1.721)	Cl—C—C: 122 (123.0) H—C—C: 124	$\mu_x = 0$ $\mu_y = 0$ $\mu_{tot} = 0$	C: -0.01 Cl: -0.11 H: +0.12
Trichloroethylene§	C—C: 1.32 (1.36) C—Cl: 1.78 (1.71 – 1.72) C—Cl: 1.77 (1.71 – 1.72) C—H: 1.08	Cl—C—Cl: 116 (117 – 123.75) H—C—Cl: 114 Cl—C ₂ —C ₁ : 124 (124) Cl—C ₁ —C ₂ : 120	$\mu_x = 0.958$ $\mu_y = 1.296$ $\mu_{tot} = 1.611$	C ₁ : +0.08 C ₂ : -0.01 Cl(C ₁): -0.08 Cl: -0.07 Cl: -0.05 H: +0.13
Tetrachloroethylene	C—C: 1.33 (1.32) C—Cl: 1.77 (1.72)	Cl—C—Cl: 115 (113.3)	$\mu_x = 0$ $\mu_y = 0$ $\mu_{tot} = 0$	C: +0.08 Cl: -0.04

*Distances are in Ångströms; angles are in degrees; dipole moments are in Debyes.

 †The ranges of experimentally-determined values are shown in parentheses. Nearly all of these are taken from Reference 39.
 ‡ μ_x and μ_y are the magnitudes of the dipole moment components in the molecular plane, parallel and perpendicular to the double bond, respectively. μ_{tot} is the magnitude of the total dipole moment.

 §The carbon bearing the greater number of chlorines is designated C₁.

¶The chlorine in question is the one that is cis to the hydrogen.

TABLE 4
CALCULATED PROPERTIES OF CHLORINATED ETHYLENE EPOXIDES*

Molecule	Structure		Dipole Moment†	Atomic Charges
	Distances	Angles		
Ethylene oxide‡	C—C: 1.49 (1.470)	C—O—C: 63	$\mu_x = 1.514$	C: -0.05
	C—O: 1.43 (1.435)	H—C—H: 115 (116.3)	$\mu_y = 0$	O: -0.21
	C—H: 1.06	H—C—C: 119	$\mu_z = 0$	H: +0.08
			$\mu_{tot} = 1.514$	
Vinyl chloride epoxide§	C—C: 1.48	C—O—C: 63	$\mu_x = 0.917$	C ₁ : +0.07
	C ₁ —O: 1.42	C ₁ —C ₂ —O: 58	$\mu_y = 1.797$	C ₂ : -0.04
	C ₂ —O: 1.44	Cl—C—H: 111	$\mu_z = 1.387$	Cl: -0.15
	C—Cl: 1.80	H—C—H: 116	$\mu_{tot} = 2.446$	O: -0.19
	C—H: 1.09	C ₁ —C ₂ —H: 119		H(C ₁): +0.11
		Cl—C—C: 120		H: +0.10
				H: +0.09
Vinylidene chloride epoxide§	C—C: 1.49	C—O—C: 63	$\mu_x = 0.551$	C ₁ : +0.17
	C ₁ —O: 1.41	O—C ₁ —C ₂ : 60	$\mu_y = 0$	C ₂ : -0.03
	C ₂ —O: 1.44	Cl—C—Cl: 113	$\mu_z = 2.414$	Cl: -0.09
	C—Cl: 1.79	H—C—H: 116	$\mu_{tot} = 2.476$	O: -0.17
	C—H: 1.08	Cl—C—C: 120		H: +0.11
		H—C—C: 119		
<i>cis</i> -1,2-Dichloro- ethylene epoxide	C—C: 1.49	C—O—C: 63	$\mu_x = 0.478$	C: +0.07
	C—O: 1.43	Cl—C—H: 112	$\mu_y = 3.130$	Cl: -0.11
	C—Cl: 1.79	Cl—C—C: 122	$\mu_z = 0$	O: -0.17
	C—H: 1.08	H—C—C: 120	$\mu_{tot} = 3.167$	H: +0.12

trans-1,2-dichloro- ethylene epoxide	C—C: 1.49	C—O—C: 63	$\mu_x = 0.458$	C: +0.06
	C—O: 1.42	O—C—C: 58	$\mu_y = 0$	Cl: -0.12
	C—Cl: 1.79	H—C—Cl: 112	$\mu_z = 0$	O: -0.17
	C—H: 1.09	Cl—C—C: 121	$\mu_{tot} = 0.458$	H: +0.13
Trichloro- ethylene epoxide§	C—C: 1.50	C—O—C: 64	$\mu_x = 0.127$	C ₁ : +0.17
	C ₁ —O: 1.41	O—C ₁ —C ₂ : 59	$\mu_y = 1.379$	C ₂ : +0.06
	C ₂ —O: 1.43	Cl—C—Cl: 112	$\mu_z = 1.064$	CH(C ₁): -0.09
	C ₂ —Cl: 1.78	H—C—Cl: 113	$\mu_{tot} = 1.747$	Cl: -0.08
	C ₁ —Cl: 1.90	Cl—C ₁ —C ₂ : 119		Cl: -0.06
	C ₁ —Cl: 1.79	Cl—C ₂ —C ₂ : 122		O: -0.10
Tetrachloro- ethylene epoxide	C—C: 1.51	C—O—C: 64	$\mu_x = 0.113$	C: +0.18
	C—O: 1.43	Cl—C—Cl: 113	$\mu_y = 0$	Cl: -0.05
	C—Cl: 1.79	Cl—C—C: 121	$\mu_z = 0$	O: -0.15
			$\mu_{tot} = 0.113$	

*Distances are in Ångströms; angles are in degrees; dipole moments are in Debyes.

†Experimentally-determined data for ethylene oxide are given in parentheses. They are taken from Reference 39.

‡ μ_x and μ_z are the magnitudes of the dipole moment components in the plane of the ring, parallel and perpendicular to the C—C bond, respectively. μ_y is the magnitude of the dipole moment component perpendicular to the plane of the ring. μ_{tot} is the magnitude of the total dipole moment.

§The carbon bearing the greater number of chlorines is designated C₁.

||This is the hydrogen that is cis to the chlorine.

¶The chlorine in question is the one that is cis to the hydrogen.

Stabilities

If the epoxides are indeed formed as the first step in the metabolic process, then their stabilities might well be important factors affecting the overall biological activities of the parent chlorinated ethylenes. The easiest way to obtain some measure of their relative stabilities without entering into speculation regarding the natures of the oxygen species involved in the formation of the epoxides is by simply taking the differences

$$E_{\text{epoxide}} - E_{\text{chlorinated ethylene}}$$

The results will not be energies of reaction, of course, since the oxygen reactants are not included, but they should be useful for comparisons within the group of molecules being studied.

The energy differences defined above are listed in TABLE 5. There is remarkably little variation among them. By this measure, all the chlorinated ethylene

TABLE 5
CALCULATED STABILITIES OF CHLORINATED ETHYLENE EPOXIDES

Molecule	$E_{\text{epoxide}} - E_{\text{chlorinated ethylene}}$ (kcal/mol)
Ethylene oxide	-46763.
Vinyl chloride epoxide	-46762.
Vinylidene chloride epoxide	-46761.
cis-1,2-Dichloroethylene epoxide	-46761.
trans-1,2-Dichloroethylene epoxide	-46762.
Trichloroethylene epoxide	-46761.
Tetrachloroethylene epoxide	-46762.

epoxides are less stable than ethylene oxide by at least 1.2 kcal/mol, but the largest difference between any two of them is only about 1 kcal/mol.

It has been suggested that the unsymmetrically-substituted epoxides may be less stable than the symmetrical ones.¹⁶ No such pattern is apparent in TABLE 5, however, nor is there any obvious correlation with the mutagenic or carcinogenic activities of the molecules.

Although the natures of the oxygen species that participate in the epoxidation processes have not been established, it may be of interest to give our calculated energy changes for two possibilities, singlet oxygen atoms and singlet oxygen molecules. Taking vinyl chloride as an example,



Charge Distributions

An indication of the charge distributions in the chlorinated ethylenes and their epoxides can be obtained from their calculated dipole moments and atomic

charges. The latter, which were obtained by the Mulliken population analysis procedure,²³ give a much more detailed picture; however, the limitations associated with the concept of atomic charge must be kept in mind.²⁴⁻²⁶ These data are all included in TABLES 3 and 4.

The general trends shown by the atomic charges can readily be summarized. Starting with ethylene, in which the carbons are negative to the extent of about -0.13 , and proceeding to its chlorinated (nonepoxide) derivatives, it is seen that the substitution of a chlorine changes the charge on the carbon involved to nearly zero. A second chlorine on the same carbon makes it definitely positive, in the neighborhood of $+0.08$. These effects are, of course, consistent with the high electronegativity of chlorine. The hydrogens also become more positive as the number of chlorines increases, but by a lesser amount, reaching a maximum of $+0.13$ in trichloroethylene. The chlorines themselves are negative, but decreasingly so as their number increases, going from -0.15 in vinyl chloride to -0.04 in tetrachloroethylene. Looking at the carbons as potential reaction sites, the most negative ones are in ethylene, vinyl chloride, and vinylidene chloride; the most positive ones are in tri- and tetrachloroethylene, and again in vinylidene chloride, which shows the largest charge separation between the carbons.

When the oxygen is added in forming the epoxides, its main effect upon the charge distribution is to attract negative charge from the two carbon atoms, in roughly equal amounts. The chlorines and hydrogens are only very slightly affected. The amount of negative charge gained by the oxygen decreases as the number of chlorines in the molecule increases; thus, the net oxygen charge goes from -0.21 in ethylene oxide to -0.15 in tetrachloroethylene oxide.

The combination of the chlorines and the oxygen produces some significantly positive carbons in the epoxides of vinylidene chloride, trichloroethylene, and tetrachloroethylene. All of these contain carbons with charges of approximately $+0.17$, which might be expected to be particularly reactive toward nucleophiles. If the interactions of epoxides with cellular macromolecules involve nucleophilic sites on the latter (as has been shown for diol epoxide (2)⁷⁻¹¹), then the markedly positive character of at least one of the carbons in each of these three epoxides might be a factor in the carcinogenic activity they show. On the other hand, the epoxide of vinyl chloride, the most potent carcinogen in this group of molecules, does not have a carbon that is positive to the same extent. Furthermore, in the hydrolyses of the vinyl chloride and trichloroethylene epoxides, which would be expected to occur via nucleophilic attack, the ring openings are found to occur at the less positive carbons.²⁷

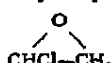
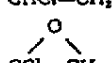
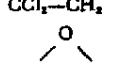
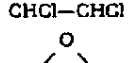
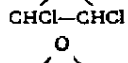
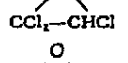
Epoxide C—O Bond Strengths

Since the carcinogenic modes of action of the chlorinated ethylenes may involve ring opening, through C—O bond cleavage, in their metabolically-produced epoxides, it would be highly desirable to know how the strengths of these C—O bonds vary with the number and location of chlorine substituents. It has long been recognized that the bond lengths for a series of bonds between the same two atoms provide a useful qualitative measure of the relative bond

strengths.³⁰ A theoretical quantity that can also be used (cautiously) as a qualitative indication of the strengths of bonds between a given pair of atoms is the overlap population, which is calculated from a molecular wavefunction.³¹ The stronger the bond, the greater its overlap population and the shorter its bond length should be. Our calculated bond lengths and overlap populations for the C—O bonds in the chlorinated ethylene epoxides are given in TABLE 6.

On the whole, both these measures of bond strength show the same general features. In the first three molecules—ethylene oxide, vinyl chloride epoxide, and vinylidene chloride epoxide—there is a very clear pattern: substitution of a

TABLE 6
CALCULATED PROPERTIES OF EPOXIDE C—O BONDS

Molecule	Formula	Bond*	Bond Length†	Overlap Population
Ethylene oxide		C—O	1.431	0.4080
Vinyl chloride epoxide		C ₁ —O	1.419	0.4193
		C ₂ —O	1.441	0.3958
Vinylidene chloride epoxide		C ₁ —O	1.409	0.4267
		C ₂ —O	1.444	0.3888
<i>cis</i> -1,2-Dichloroethylene epoxide		C—O	1.425	0.4078
<i>trans</i> -1,2-Dichloroethylene epoxide		C—O	1.423	0.4089
Trichloroethylene epoxide		C ₁ —O	1.413	0.4184
		C ₂ —O	1.433	0.3980
Tetrachloroethylene epoxide		C—O	1.431	0.4020

*The carbon bearing the greater number of chlorines is designated C₁.

†Bond lengths are in Angstroms.

chlorine for a hydrogen strengthens the C—O bond in which that carbon participates and weakens the other C—O bond. Thus, vinyl chloride epoxide and, even more, vinylidene chloride epoxide have one relatively strong and one relatively weak C—O bond. The C—O bonds in the epoxides of both *cis*- and *trans*-1,2-dichloroethylene have the same properties, of course, and, since there is a chlorine substituted on each carbon, the strengthening and weakening effects oppose each other. There is certainly no net weakening of these C—O bonds relative to ethylene oxide. When a third chlorine is substituted into either of these molecules, producing trichloroethylene epoxide, the same result is observed as

before: one C—O bond becomes stronger, the other weaker. The epoxide of tetrachloroethylene is again symmetrical in structure, but the C—O bonds are apparently weaker than those in the other symmetrically-substituted molecules, the 1,2-dichloroethylene epoxides, and perhaps even weaker than those in ethylene oxide.

The data in TABLE 6 indicate that, in the three unsymmetrically-substituted epoxides—those of vinyl chloride, vinylidene chloride, and trichloroethylene, it is the C—O bond involving the less-substituted carbon that is the weaker of the two. This conclusion is fully consistent with the previously-mentioned experimental observations that it is this bond that is broken in the hydrolyses and thermolyses of vinyl chloride epoxide and trichloroethylene epoxide.^{21,22}

Furthermore, it is notable that the three unsymmetrically-substituted epoxides plus tetrachloroethylene epoxide are, apparently, the ones with the weakest C—O bonds; their parent chlorinated ethylenes are also the ones showing carcinogenic activity (see TABLE 2). This is consistent with the concept that this activity involves the opening of a C—O bond in the process of interacting with a cellular macromolecule.

SUMMARY

This paper has presented the initial results of a computational study of the chlorinated ethylenes and their epoxides. Particular attention was devoted to those properties which may be related to the reactivities, and specifically carcinogenicities, of these molecules. Detailed calculations of their optimum structures have been carried out, and stabilities, dipole moments, charge distributions, and epoxide C—O bond strengths were determined and have been discussed. For the epoxides, most of this information, including the structural data, has not previously been available. It is hoped that this will help to bring about a better understanding of the biological activities of the chlorinated ethylenes, and of the manner in which these activities are related to the numbers and locations of the chlorine substituents. Particularly promising in this respect are the qualitative assessments of the epoxide C—O bond strengths presented above. More quantitative measures of this key property are currently being computed.

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DISCUSSION

J. SNYDER (H. C. Ørsted Institute, Copenhagen): You suggested that the carcinogenicity of these molecules was conceivably related to the positive charge calculated as a consequence of chlorine substitution, that, therefore, if the ring opening was stimulated by nucleophilic attack, a nucleophile might be directed to those centers with the greatest degree of positive charge. Are there kinetic data on well-behaved nucleophilic attacks on this particular set of molecules so one can correlate rates with charge?

POLITZER: Yes. There's one such set of kinetic measurements, but it doesn't correlate with charge. I qualified the lack of correlation by pointing out that charge is obviously not the only factor. In the case of triethylene epoxide, it's known that the bond that opens is the one that does not have the two chlorines and, therefore, is not the more positive one. It would also depend on the nature of the transition state. If it were an S_N1 kind of reaction, it would hold, but if it were a nucleophilic attack, then a nucleophile would attack the carbon that's least sterically hindered.

SNYDER: Yes, that's the argument, that it's a matter of hindrance.

L. ALLEN (Princeton University, Princeton, N.J.): It seems to me that I remember an article about two years ago in the Journal of the American Chemical Society, by, I think, Olsen of Staten Island College, who did some evaluations of epoxides to find the bond-strengths. I think these results would be a worthwhile point of reference. Also, I suggest that you'd find that orbital analysis tends to accentuate the effects.

W. LIPSCOMB (Harvard University, Cambridge, Mass.): In the case of vinyl chloride, which is rather more carcinogenic than the others, I want to suggest the possibility that, after the epoxide or the dihydroxide is formed, the leaving of the chloride ion could generate an electrophile. That carbon-chlorine distance is longer than all the other carbon-chlorine distances in the chloroethylenes, and the chloride would be more ready to leave. This might be one way for more specific activity of chloroethylene than of the others.

POLITZER: I think that's a good suggestion. There is also the fact that the chlorines are known to rearrange in those compounds as you may have seen in the metabolic pathways, so there's a good chance that something of that sort might be happening.

UNIDENTIFIED SPEAKER: I think the problem might be clarified considerably if you look at another series of substituted ethylenes. It's very hard to judge substituent effects from a single substituent, and if you did some calculations on methylethylenes, cyanoethylenes, and methoxyethylenes, as well as the chlorine, and then looked at the extensive kinetic data available in the literature on both the open-ended protonated and the ordinary oxides, you would have a much better idea of the substituent effects.

W. GODDARD (*California Institute of Technology, Pasadena*): It seems to me that it's a long shot to look at the properties of the ground state of the species to get information about the chemistry. It seems to me that it would be better to look at some of the processes that might happen with the protonation, at the addition of the water to the protonated form, and see how the presence of chlorines affects barriers or other aspects of the potential surfaces.