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Reactive Properties of *trans*-Dichlorooxirane in Relation to the Contrasting Carcinogenicities of Vinyl Chloride and *trans*-Dichloroethylene

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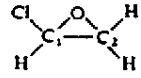
Abstract

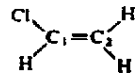
Our objective in this work is to gain insight into the contrasting carcinogenic activities of vinyl chloride (definitely carcinogenic) and *trans*-dichloroethylene (apparently inactive). The initial metabolic step for each molecule is believed to be epoxidation of the double bond, and there is evidence indicating that for vinyl chloride, this epoxide (chlorooxirane) is its ultimate (direct-acting) carcinogenic form. This article presents the findings of a computational study of the reactive properties of *trans*-dichlorooxirane (the epoxide of *trans*-dichloroethylene). An *ab initio* SCF-MO procedure was used to determine the energy requirements for stretching the C—O and C—Cl bonds (S_N1 reactivity) and to study the epoxide's S_N2 interactions with ammonia, taken as a model nucleophile. The starting points were the oxygen- and chlorine-protonated forms of the epoxide. The structure of the system was reoptimized at each step along the various reaction pathways. The results of this work are compared to an analogous earlier study of the reactive properties of chlorooxirane. The chlorine-protonated C—Cl bonds are found to have much lower energy barriers to stretching than do the oxygen-protonated C—O bonds. In the S_N2 processes, intermediate complexes are formed with ammonia by both the oxygen- and the chlorine-protonated epoxides; the latter complexes are the more stable. Based on our results, we propose two mechanisms (one S_N1 and the other S_N2) whereby *trans*-dichlorooxirane can interact with N_7 of guanine to produce an adduct analogous to one formed by chlorooxirane, which has been found to be the primary *in vivo* DNA alkylation product of vinyl chloride and to which has been attributed the carcinogenicity of the latter. Overall, *trans*-dichlorooxirane is found to be chemically more reactive than chlorooxirane; this may help to account for the much lesser carcinogenic and mutagenic activities of *trans*-dichloroethylene, since the epoxide may be reacting with other cellular nucleophiles before it reaches the key site(s) at which the carcinogenic or mutagenic interaction would occur. We also offer some speculations concerning other possible factors related to the differing carcinogenicities of vinyl chloride and *trans*-dichloroethylene, such as ease of epoxide formation and the likelihood of oxygen protonation.

1. Introduction

We have recently carried out a computational study of the reactive behavior of chlorooxirane (I), which is the epoxide that is formed from vinyl chloride (II) [1]. This epoxide, which can be produced metabolically



I



II

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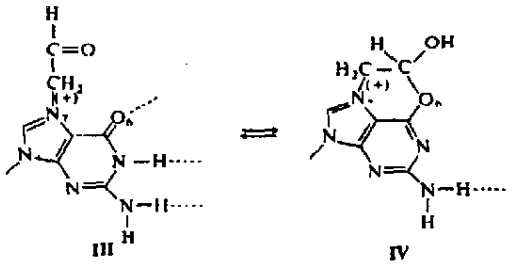
by the mixed function oxidase system [2–6], is known to be a strong mutagen [2, 5, 7], and is believed to be a direct-acting carcinogen [3, 5–8], responsible for the well-established carcinogenicity of vinyl chloride [2, 9–12].

Chlorooxirane is known to alkylate various nucleic acid bases, RNA, DNA, and protein residues [2, 8, 13–15], forming covalent bonds to nucleophilic sites in these systems. In an important recent development [16, 17], supporting earlier work [14], it has been shown that the major *in vivo* DNA alkylation product of vinyl chloride is the 7-*N*-(2-oxoethyl) derivative of guanine, **III**:



III **IV**

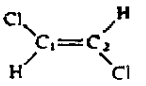
(According to some evidence, **III** may be in equilibrium with a cyclic hemiacetal (**IV**) involving O_6 [16].) It has been suggested that this oxoethyl derivative, **III**, may be responsible for the carcinogenicity of vinyl chloride [17].

The results of our earlier study allowed us to propose two possible routes for the formation of the key alkylation product, **III** [1]. One of these involves an S_N1 mechanism and starts with the chlorine-protonated form of chlorooxirane; the other is an S_N2 process that begins with the oxygen-protonated epoxide.

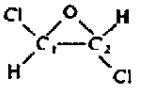
Vinyl chloride belongs to the family of chlorinated ethylenes, which has six members. The initial metabolic step undergone by each of these molecules is believed to be epoxidation of the C=C double bond [18–20]. It would now be of considerable interest to know how the reactive properties of the epoxide of a much less carcinogenic chlorinated ethylene may parallel or differ from those of chlorooxirane. Such an analysis might provide some insight into the manner in which the structural difference between the two epoxides leads to their contrasting biological activities.

It is extremely difficult to rank the carcinogenicities of the chlorinated ethylenes, since their activities, as determined by experimental tests, are highly dependent upon the species or systems being used in the tests and the specific details of the testing procedures.* It seems safe to say, however, that vinyl chloride is the most carcinogenic of them, while *trans*-dichloroethylene (**V**) appears to have little or no carcinogenic potency [18, 19, 22].

*For a more general discussion and analysis of the chlorinated ethylenes and their epoxides, see Ref. 21.

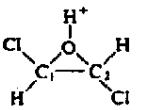


V

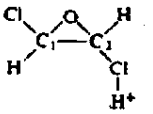


VI

Our aim in the present study accordingly has been to investigate the reactivity of *trans*-dichlorooxirane (VI) in both S_N1 and S_N2 processes, comparing it to our earlier findings for chlorooxirane [1] and relating these results to the difference in the carcinogenicities of vinyl chloride and *trans*-dichloroethylene. As in the chlorooxirane work, our starting points have been the oxygen- and chlorine-protonated forms of the epoxide, VII and VIII*:



VII



VIII

2. Methods

All of the results to be presented were obtained computationally, using, as before [1], the GAUSSIAN 70 *ab initio* self-consistent-field molecular orbital procedure [31]. First we calculated optimized geometries for *trans*-dichlorooxirane, VI (refining an earlier computed structure [21]), and its oxygen- and chlorine-protonated forms, VII and VIII. S_N1 ring opening was investigated for VII, by stretching one of the C—O bonds in incremental steps, reoptimizing the entire structure at each step. The S_N1 reactivity of the protonated C—Cl bond was studied in essentially the same manner, now using VIII.

S_N2 processes were examined using the ammonia molecule as a model nucleophile, and allowing it to approach either C_1 or C_2 in VII and C_2 in VIII. At each different C—N distance, all structural parameters were reoptimized (except for the N—H distances in the ammonia).

* The extent to which *trans*-dichlorooxirane is protonated *in vivo* is uncertain. However, there do exist subcellular regions with high proton activities [23–25], and for chlorooxirane there is some evidence suggesting that its biological activity involves a protonated form [26]. Since the enzymatic reactions involved in DNA replication are localized in the nuclear membrane, it is of particular interest that this membrane contains certain redox systems [27], and that these are believed to produce high local proton activities [25, 28, 29]. One such is the cytochrome *P*-450 system that activates some carcinogens [30].

3. Results and Discussion

A. *trans*-Dichlorooxirane and Its Protonated Forms

The computed structures and energies of *trans*-dichlorooxirane, **VI**, and its oxygen- and chlorine-protonated forms, **VII** and **VIII**, are given in Table I. All of our geometry optimization was carried out at the STO-3G level, which is known to be effective for structure calculations [32]. Using these geometries, the energies in Table I were then computed in terms of STO-6G basis sets.

Protonation at either site is highly favorable energetically, with the oxygen being preferred; our STO-6G proton affinities are 203 kcal/mole for the oxygen and 160 kcal/mole for the chlorine. These are both somewhat smaller than our corresponding values for chlorooxirane, 216 and 169 kcal/mole [33].

The major structural effect of oxygen protonation is an increase in the lengths of the C—O bonds, from 1.43 to 1.50 Å. This reflects the well-established weakening of the C—O bonds that is known to accompany oxygen protonation of epoxides [33–37]. Consistent with this, we found the calculated force constants of the C—O bonds to decrease from 8.9 to 7.0 mdyn/Å. We observed earlier that this C—O bond weakening occurs to a greater extent when the carbon bears a chlorine [33]. Our present results are fully in agreement with this conclusion; the effects that we observe are similar to what was found for the C_1—O bond in oxygen-protonated chlorooxirane, and greater than the weakening of the C_2—O bond in the latter, or of the C—O bonds in protonated ethylene oxide, **IX** [33].

Chlorine protonation has more dramatic structural effects (Table I). The most striking of these is the lengthening of the C_2—Cl bond from 1.79 to 2.04 Å, indicating a considerable weakening of this bond. (Its force constant changes from 5.3 to 1.8 mdyn/Å.) This is accompanied by a marked shortening of the C_2—O bond, to 1.37 Å, as well as significant changes in the bond angles around C_2. Thus, as in the case of chlorooxirane [33], protonation of a chlorine can be regarded as introducing a tendency toward the loss of HCl and the development of C_2—O double bond character. Very definite indications of these trends will be seen when the C_2—Cl bond is stretched in studying its S_N1 reactivity.

B. S_N1 *Processes*

C—O bonds. To simulate S_N1 ring opening, one of the C—O bonds in oxygen-protonated *trans*-dichlorooxirane, **VII**, was stretched in a series of four steps, the entire structure being reoptimized at each point. The relative STO-3G energies of the reoptimized system after each step are presented in Table II. (All of the interaction energies that will be given in the remainder of this paper will have been calculated at the STO-3G level.)

The energy required to stretch either C—O bond from its equilibrium length, 1.50 Å, to an arbitrarily selected 2.20 Å is 31 kcal/mole. This is virtually the same energy requirement as was found for extending the C_1—O bond in oxygen-protonated chlorooxirane (**XII**) by 0.70 Å, and is considerably less than the 44 kcal/mole needed for its C_2—O bond [1]. (We have found the corresponding

TABLE 1. Calculated structures and energies.

Molecule	Energy, STO-6G (hartrees)	Distances (Å)	Angles (degrees)
trans-Dichlorooxirane	−1067.201	C—O: 1.43 C—C: 1.49 C—Cl: 1.79 C—H: 1.09	O—C—C: 59 Cl—C—C: 120 H—C—C: 121 H—C—Cl: 112
Oxygen-protonated *trans*-dichlorooxirane	−1067.524	C—O: 1.50 C—C: 1.50 C—Cl: 1.76 C—H: 1.10 O—H$^+$: 1.00	O—C—C: 60 Cl—C—C: 121 H—C—C: 120 H—C—Cl: 116 H$^+$—O-ring plane:[a] 119
Chlorine-protonated *trans*-dichlorooxirane[b]	−1067.456	C_1—O: 1.45 C_2—O: 1.37 C_1—C_2: 1.49 C_1—Cl: 1.77 C_2—Cl: 2.04 C_1—H: 1.10 C_2—H: 1.10 Cl—H$^+$: 1.35	O—C_1—C_2: 55 O—C_2—C_1: 61 Cl—C_1—C_2: 119 H—C_1—C_2: 120 H—C_1—Cl: 115 Cl—C_2—C_1: 113 H—C_2—C_1: 137 H—C_2—Cl: 101 H$^+$—Cl—C_2: 104
Ammonia complex of oxygen-protonated *trans*-dichlorooxirane[c]	—	C_1—O: 2.32 C_2—O: 1.40 C_1—C_2: 1.56 C_1—Cl: 1.79 C_2—Cl: 1.84 C_1—H: 1.10 C_2—H: 1.10 O—H$^+$: 0.99 C_1—N: 1.54	O—C_1—C_2: 36 O—C_2—C_1: 103 Cl—C_1—C_2: 112 H—C_1—C_2: 110 H—C_1—Cl: 110 Cl—C_2—C_1: 108 H—C_2—C_1: 112 H—C_2—Cl: 108 H$^+$—O—C_1: 144 N—C_1—C_2: 111
Ammonia complex of chlorine-protonated *trans*-dichlorooxirane[d]	—	C_1—O: 1.43 C_2—O: 1.42 C_1—C_2: 1.50 C_1—Cl: 1.79 C_2—Cl: 3.51 C_1—H: 1.10 C_2—H: 1.09 Cl—H$^+$: 1.32 C_2—N: 1.53	O—C_1—C_2: 58 O—C_2—C_1: 59 Cl—C_1—C_2: 119 H—C_1—C_2: 120 H—C_1—Cl: 113 Cl—C_2—C_1: 88 H—C_2—C_1: 127 H—C_2—Cl: 46 H$^+$—Cl—C_2: 168 N—C_2—C_1: 114

[a] The angle between the O—H$^+$ bond and the ring plane in oxygen-protonated *trans*-dichlorooxirane is 119°.

[b] C_2 is the carbon bearing the protonated chlorine.

[c] The ammonia is interacting with C_1.

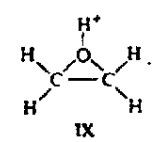
[d] The ammonia is interacting with C_2, which is the carbon bearing the protonated chlorine.

TABLE II. Calculated relative energies for bond-stretching processes.[a]

Oxygen-protonated *trans*-dichlorooxirane							
C—O bond							
Bond length (Å)	1.50	1.60	1.75	1.90	2.20		
Relative energy[a] (kcal/mole)	0.0	1.2	13.0	22.9	30.8		
Chlorine-protonated *trans*-dichlorooxirane							
C_2—Cl bond[b]							
Bond length (Å)	2.04	2.20	2.50	2.75	3.00	3.25	3.50
Relative energy[a] (kcal/mole)	0.0	0.9	3.0	4.1	5.0	5.8	6.4

[a] These energies have all been computed at the STO-3G level.
[b] C_2 is the carbon bearing the protonated chlorine.

value in protonated ethylene oxide, IX, also to be 44 kcal/mole.) Thus, the presence of a chlorine substituent on the carbon clearly increases the ease of opening these C—O bonds via S_N1 processes.

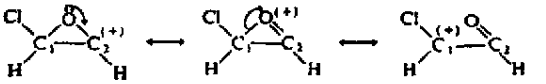


IX

The primary structural change that accompanies the lengthening of one of the C—O bonds in VII, say C_1—O, is that the other carbon (C_2) assumes a more tetrahedral configuration; most of its bond angles are now in the 110°–112° range. The lengths of its bonds also change somewhat, in the direction of their normal single bond values. The only other notable feature is that the C_1—Cl distance decreases from 1.76 to 1.70 Å. As has been found in previous studies of protonated epoxides [1, 34], an analysis of the atomic charges, obtained by the population analysis procedure [35], shows the bond opening to have a $C^{+\delta}\cdots O^{-\delta}$ character.

C—Cl bonds. The energies associated with stretching the C_2—Cl bond in chlorine-protonated *trans*-dichlorooxirane (VIII) and reoptimizing the structure after each step are also given in Table II. Only about 6 kcal/mole are required for a very considerable lengthening of this bond, from 2.04 to 3.50 Å. This confirms the discussion earlier in this paper concerning the weakening of the C—Cl bond that results from protonation of the chlorine; a similar effect was observed for chlorooxirane, for which the corresponding energy requirement was 4 kcal/mole [1]. (The importance of protonation in weakening the C—Cl bond can be seen from our finding that an energy input of 118 kcal/mole is needed to stretch this bond in unprotonated chlorooxirane from 1.80 to 3.00 Å.)

The extension of the C_2—Cl bond to 3.50 Å can be regarded as nearly equivalent to removing the HCl (the sum of the van der Waals radii of carbon and chlorine is about 3.5 Å [36]), and the calculated atomic charges show that it comes off as a neutral entity. The positive charge on the resulting carbonium ion, **Xa**, can be delocalized by contributions from resonance structures **Xb** and **Xc**. Consistent with this resonance picture are the facts that



Xa **Xb** **Xc**

the stretching of the C_2—Cl bond is accompanied by a shortening of the C_2—O distance to 1.28 Å (which is approaching the standard $\geq C{=}O$ double bond value of 1.21 Å [37]) and a lengthening of the C_1—O bond from 1.45 to 1.51 Å.

C. S_N2 *Processes*

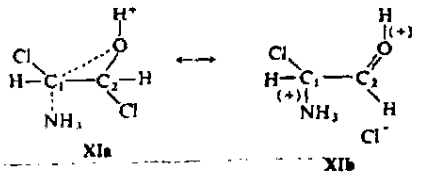
Interaction of ammonia with oxygen-protonated *trans*-dichlorooxirane. An NH_3 molecule was allowed to attack C_1 in **VII** with complete freedom regarding its line and angle of approach. At each of several different C_1—N distances, the structure of this system was reoptimized (except for the N—H bond lengths, which were kept at their equilibrium ground-state values).

TABLE III. Calculated interaction energies for reactions with ammonia.[a]

	Oxygen-protonated *trans*-dichlorooxirane					
C—N distance (Å)	3.00	2.50	2.20	2.00	1.80	1.54
Interaction energy[a] (kcal/mole)	−11.1	−11.5	−10.6	−31.5	−66.3	−87.8
	Chlorine-protonated *trans*-dichlorooxirane					
C_2—N distance (Å)[b]	3.50	3.00	2.20	1.80	1.53	
Interaction energy[a] (kcal/mole)	−9.6	−23.9	−35.8	−77.8	−98.0	

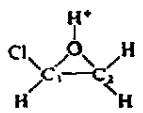
[a] These energies have all been computed at the STO-3G level.
[b] C_2 is the carbon bearing the protonated chlorine.

A stable intermediate complex, **XIa**, was obtained, in which the nitrogen is in the plane of the three-membered ring. The optimized geometry of this complex is reported in Table I. Table III shows the interaction energies as the NH_3 approaches C_1; the line of approach was initially approximately perpendicular to the C_1—C_2 bond, but the N—C_1—C_2 angle eventually widened to 111°.



XIa XIb

The calculated interaction energy, −88 kcal/mole, is very similar to the −87 kcal/mole computed for the reaction of NH_3 with C_2 in oxygen-protonated chlorooxirane, XII, and significantly more than the −73 kcal/mole that was obtained for reaction at C_1 in the latter molecule [1].



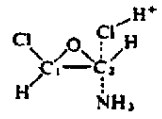
XII

It appears, therefore, that the reaction of NH_3 at one of the carbons is favored by the presence of a chlorine on the other carbon. This may be due to the stabilizing effect of some degree of double bond formation, reflecting a contribution from structure XIb, in which the chlorine on C_2 has come off as a negative ion. This interpretation is supported by the observed shortening of the C_2—O bond during the course of the reaction of NH_3 at C_1, and the lengthening of the C_2—Cl bond (Table I).

An important aspect of the process forming the complex represented by XIa and XIb is that it involves a substantial opening of the epoxide ring, as the C_1—O distance increases to 2.32 Å. This is accompanied by an inversion of the hydrogen and chlorine on C_1, and a general tendency toward tetrahedral configurations around both carbons and normal single bond lengths.

The data in Table III show that a small energy barrier is encountered in the formation of this complex; it comes in the neighborhood of a C_1—N separation of 2.2 Å. A similar phenomenon was observed in our earlier study of chlorooxirane [1], and we believe that the same explanation is applicable here: there appears to be some degree of hydrogen bonding between the proton and the chlorine on C_1 in oxygen-protonated *trans*-dichlorooxirane (VII). As the C_1—O bond lengthens in the course of the interaction with ammonia, this hydrogen bonding is disrupted, giving rise to the observed energy barrier. Supporting this interpretation are the calculated Cl—H^+ separation in VII, 2.77 Å, which is consistent with the existence of this type of hydrogen bond [38], and also the variation of the computed charge on the proton; this initially decreases very gradually as the NH_3 approaches, until a C_1—N separation of 2.20 Å is reached, at which point it drops sharply from +0.34 to +0.26 (between 2.20 and 2.00 Å).

Interaction of ammonia with chlorine-protonated *trans*-dichlorooxirane. The reaction of NH_3 with C_2 of the chlorine-protonated *trans*-dichlorooxirane (VIII) produces the intermediate complex XIII, the structure of which is given in Table I. The HCl has essentially been driven off, leaving as a neutral species; much of the positive charge of the system has been acquired by the ammonia hydrogens, each of which has become more positive by about 0.18 electron units. The epoxide ring remains intact, although the hydrogen on C_2 has undergone an inversion.

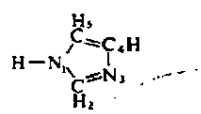


XIII

As was found for the analogous process involving chlorooxirane [1], this interaction gives a more stable intermediate (XIII) than is obtained with the oxygen-protonated epoxide, the stabilization energy being −98 kcal/mole (Table III). An interesting point is that the preferred initial approach of the ammonia is toward the hydrogen of the C_2—H bond. This may reflect some degree of weak N···H hydrogen-bonding, since the C_2—H bond simultaneously lengthens from 1.10 to 1.35 Å. When the C_2—N separation is somewhere in the neighborhood of 2.5 Å, however, the line of approach shifts toward C_2 and the C_2—H bond length returns to a normal value. (Similar behavior was observed in our study of the interaction between ammonia and chlorine-protonated chlorooxirane [1].)

D. Imidazole as the Nucleophile

In order to determine whether our conclusions would be significantly affected if a bulkier nucleophile, with somewhat different electronic properties, were used, we repeated some of the preceding calculations with N_3 of imidazole (XIV) serving as the nucleophile. (Imidazole can be viewed as a model for the five-membered ring in both adenine and guanine.)



XIV

A comparison between the ammonia and the imidazole results was made for both the oxygen- and the chlorine-protonated forms of *trans*-dichlorooxirane and also chlorooxirane. In each instance, the imidazole was initially placed so that the C—N_3 distance was equal to the C—N bond length in the optimized equilibrium ammonia complex. Then the geometry of the epoxide portion of the

system and the orientation of the imidazole were reoptimized. (The structure of the latter was not varied.)

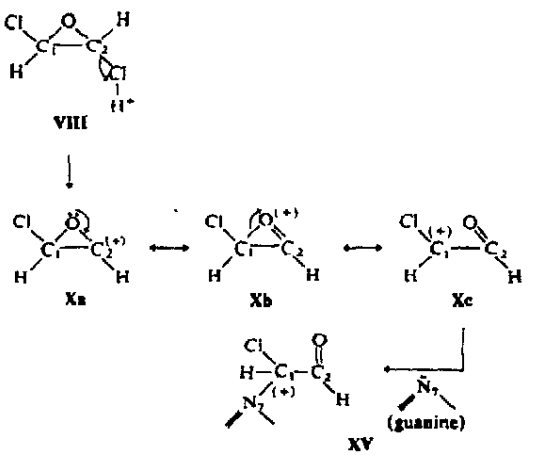
We found very little change in the structural parameters that were being recomputed, which suggests that no key steric factors are being overlooked, at least in the present calculations, by using ammonia as the nucleophile. However, the interactions are consistently more stable when imidazole is involved, by roughly 20 kcal/mole; this effect is slightly greater for *trans*-dichlorooxirane than for chlorooxirane. In keeping with this observation, the optimized C—N distances are approximately 0.03 Å shorter for imidazole than for ammonia.

On the whole, the imidazole results provide some reassurance that ammonia is a reasonable model system to use for our present purposes.

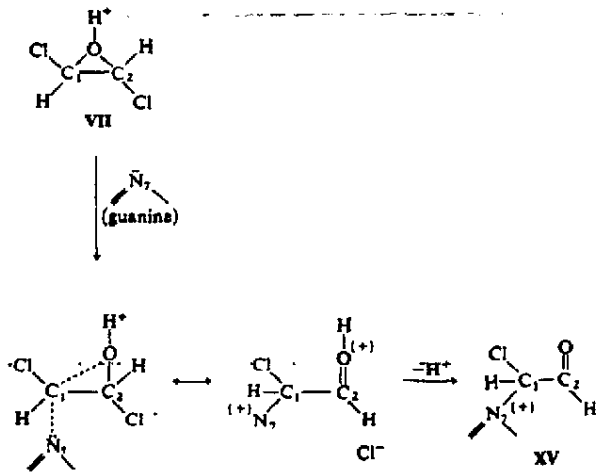
E. Possible Reaction Pathways to DNA Adduct

In our earlier study of chlorooxirane [1], we found two possible reaction pathways whereby this epoxide could interact with N_7 of guanine to form the key 2-oxoethyl derivative (III) that has been proposed as being responsible for the carcinogenicity of vinyl chloride [17].

The results of our present investigation of *trans*-dichlorooxirane reactivity indicate that analogous routes are available to this epoxide as well. The first is an S_N1 process that starts with the chlorine-protonated form of *trans*-dichlorooxirane. It was shown in Section 3B that very little energy is required to remove HCl from this system, leaving behind the positively charged species that is described by structures Xa–Xc. The N_7 position of guanine, which is highly nucleophilic [39], could then react with C_1 to yield XV (see below), which is the analog, in the present context, of III. The whole process can be summarized as follows:



The second possible process leading to XV involves an S_N2 mechanism, which starts with oxygen-protonated *trans*-dichlorooxirane and proceeds through an intermediate analogous to that described earlier in this article by resonance structures XIa and XIb:



Thus, starting with the epoxide metabolite of *trans*-dichloroethylene, we can account—by either of two mechanisms—for the formation of a DNA alkylation product, XV, which is the analog of the one (structure III) that has been proposed as being the key carcinogenic DNA adduct produced by vinyl chloride [17]. (It should be pointed out, however, that even if this interpretation of the role of III does prove to be correct, it does not necessarily follow that XV, with its chlorine substituent, can fulfill a similar function.)

F. Chemical Reactivities of Chlorooxirane and trans-Dichlorooxirane, and Speculation Concerning Their Contrasting Carcinogenic Activities

Our results indicate that protonated *trans*-dichlorooxirane is significantly more reactive than protonated chlorooxirane, in both S_N1 and S_N2 processes. We have shown that ring opening via the breaking of a C—O bond in the oxygen-protonated epoxide can take place as easily for either C—O bond in *trans*-dichlorooxirane as for the more reactive of the two C—O bonds in chlorooxirane. Protonation of chlorine produces C—Cl bonds of essentially equal reactivities in the two epoxides, but there are two such possibilities in *trans*-dichlorooxirane and only one in chlorooxirane.

Another result of the structural difference between these two molecules is that oxygen protonation should be less likely for *trans*-dichlorooxirane than for chlorooxirane; this follows from both the lower oxygen proton affinity of the

former (Section 3A) and also the fact that it has two chlorines competing with the oxygen for the proton, whereas chlorooxirane has only one.*

If the carcinogenic pathways of these molecules do involve the adducts III and XV, and if they are S_N2 processes (for which there is some support [42, 43]), then our results indicate that it is the oxygen-protonated epoxides that should be the starting points. Thus, the lesser probability of *trans*-dichlorooxirane undergoing oxygen protonation may be a factor in its low level of carcinogenic activity.

A second possible factor is related to our finding that, once protonated, *trans*-dichlorooxirane is more reactive than protonated chlorooxirane. This may considerably increase the likelihood of the former reacting with other cellular nucleophiles before it reaches the key site(s) at which the mutagenic or carcinogenic interaction would occur. Such a situation is known to exist in the case of the *syn* and *anti* 7,8-dihydrodiol-9,10-epoxides of benzo[*a*]pyrene; the *syn* isomer is the more chemically reactive, but the *anti* is the more carcinogenic [44–46].

Another point to consider is the ease of formation of the epoxides themselves. In a previous study [47], we have shown that the electrostatic potential in the π-bond region is considerably less negative for *trans*-dichloroethylene than it is for vinyl chloride. If the metabolic epoxidation that these molecules undergo involves interaction with an electrophilic oxygen species, as has been proposed,† then the electrostatic potentials suggest that this might take place less readily for *trans*-dichloroethylene. Since the formation of the epoxide is believed to be a necessary step in whatever carcinogenesis does occur (see Section 1), such differing tendencies for epoxidation could be another element in the contrasting carcinogenic activities of these two chlorinated ethylenes.

Finally, it is interesting to speculate briefly concerning the functioning of the adduct III, proposed as a critical intermediate in the carcinogenic action of vinyl chloride [17]. If III is indeed in an equilibrium with a hemiacetal involving O_6 of guanine [16], then this would be expected to significantly affect the guanine–cytosine hydrogen bonding, as can be seen from a comparison of structures III and IV. This could lead to miscoding [6, 15, 45], and the possibility of replicational and transcriptional errors [16, 49] and the development of tumors. Such an equilibrium would be consistent with recent findings indicating that interaction with O_6 of guanine plays a key role in some carcinogenic processes [50–52]. It would be of interest to determine the tendency (if any) of the *trans*-dichlorooxirane adduct XV to enter into an analogous equilibrium with a hemiacetal; this might serve to further clarify the reasons for the differing carcinogenicities of vinyl chloride and *trans*-dichloroethylene. Such a study is presently underway.

* We have also found the electrostatic potential associated with the oxygen to be less negative in *trans*-dichlorooxirane than in chlorooxirane [40]; this is a good indication of the relative tendencies toward protonation [41].

† For a discussion of this point, see Ref. 48.

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