4. Other Research

Ab initio MO studies on allylic chloropropenes

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Research Organization
Special Research Projects
Theme Studies on exposure to halogenated organic compounds and its human health effects

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Background

Electronic structures of carcinogenic and mutagenic compounds have been investigated by many researchers using molecular orbital(MO) calculations.[1-8] The pioneering application of MO theory to study a chemical carcinogenesis was the work of the Pullmans on the electronic structures of polycyclic hydrocarbons, that is well known K and L regions theory.[9-11] Other large part of application for exploring carcinogenicity and mutagenicity was investigations of pairing interactions between nucleic acid bases and mispairing between nucleic acid bases and base-analogous speciesa.[12-15]

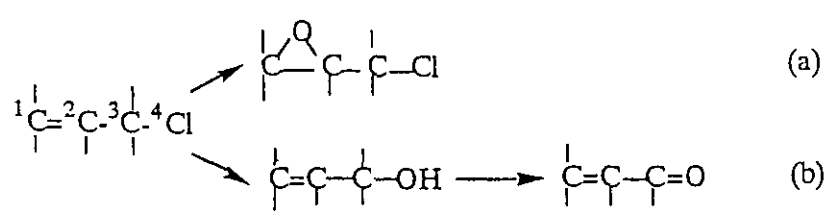
During last ten years the development of the electronic computer and the revision and refinement of programs for ab initio molecular orbital calculations, such as GAUSSIAN series, make us handle the rather large biological molecules easily.

On the other hand, chlorinated organic compounds have been of interesting due to their carcinogenic and mutagenic activities.[16-19] Allylic chloropropenes are an important species among them, some of which have been studied of their mutagenicity and carcinogenicity.[17,19] Allylchloride and 1,3-dichloropropene have proved to be carcinogenic in mice.[20]

Under the situation calculating the electronic structures of allylic chloropropenes by the use of MO method and providing the theoretical explanation of their carcinogenic and mutagenic processes seem to be pointed out a new strategy with computational technique.

Object

Neudecker and Henschler treated the mutagenicity of allylic chloropropenes by the metabolic activation process in the presence of rat-liver homogenate fraction(S9mix).[21] In the study they used the enzyme inhibitors which confirm the metabolic activation intermediates in the mutagenic reaction. From the results in their study, in which the six chloropropenes, allylchloride(1), 2,3-dichloro-1-propene(2), 1,3-dichloropropene(3), 1,1,2,3-tetrachloro-2-propene(4), 1,2,3-trichloropropene(5) and hexachloropropene, have been treated, two



Scheme 1. Metabolic activation pathways of allylic chloropropenes in S9mix. (a) is epoxidative pathway and (b) is hydrolytic-oxidative pathway.

metabolic pathways as shown in Scheme 1 were found. (a) in the scheme is epoxidative pathway and (b) hydrolytic-oxidative pathway. Ultimate mutagenic intermediates in the pathways are epoxide and acrolein, respectively. The six allylic chloropropenes were classified into three categories; first group including 2 and 4 is activated through epoxidative pathway, second group of 1 and 3 through hydrolytic-oxidative pathway and third group of 5 through both pathways. It is especially pointed out that chlorine substitution at the center carbon atom in C=C-C skelton brings the electron deficiency of the atom because of -I effect of substituent and therefore they are more facile to be activated through epoxidative pathway.

In the present study ab initio MO calculation has been performed to obtain the electronic structures of five allylic chloropropenes(1-5) and to discuss the computational results by comparing with the experimental.

Methods of Calculation

Geometrical optimization was performed with HF/STO-3G, HF/6-31G** and MP2/6-31G** methods. The potential energy profiles with respect to the C-Cl(---H$^+$) bond length in the protonated allylic chloropropenes were evaluated by the use of HF methods with both STO-3G and 6-31G** basis sets, because the cleavage of terminal C-Cl bond brings the allyl cation, C=C-C$^+$, which seems to be ultimate calcinogenic comound binding to DNA. All calculations were performed with the Gaussian 92 program package installed in NEC SX-3 computer.

Results

Geometry: Allylic chloropropenes seem to be four local stationary conformations with respect to the rotation around the C-C single bond. Therefore four cases of initial conformation in each compound have been examined as shown in Fig. 1. The results are shown in Table 1. The most stable conformation in each molecule slightly changes in one method to another. It is noticed that in almost cases the most stable structure is conformation 4. An exception is shown in 2, and *trans* of 4 with STO-3G basis set which is not cited in the table. In three cases, *trans* of 5 in addition to two cases described above, the

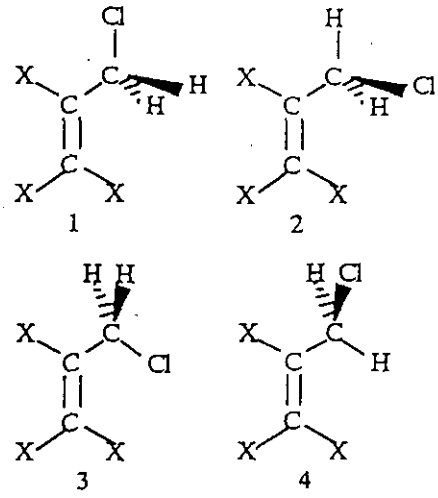


Figure 1. Four initial conformations with respect to C-C single bond rotation.

Table 1. The most stable conformation of allylic chloropropenes

	HF/6-31G**		MP2/6-31G**	
	No	E[a)]	No	E[a)]
1	4(3)	0.0020	4(3)	0.0016
2	3(4)	0.0004	4(3)	0.0001
3 (*cis*)	4(1)	0.0016	4(1)	0.0019
(*trans*)	4(3)	0.0018	4(3)	0.0018
4 (*cis*)	4(2)	0.0057	4(2)	0.0053
(*trans*)	4(3)	0.0009	4(3)	0.0015
5 (*cis*)	4(1)	0.0069	4(1)	0.0060
(*trans*)	4(3)	0.0002	4(3)	0.0007

a) E is the energy difference between the most stable conformation and the second. Unit is a.u.

energy differences between most stable conformation and the second stable one are very small. It is noteworthy that the small energy differences appear in the molecules which have the chlorine substituted into the central carbon atom.

In the MP2/6-31G** results the averaged values of calculated bond separations are 1.3392 and 1.4916A for C=C and C-C bonds, respectively. The bond separations of C-Cl bonds varyed in the wide range, 1.71A to 1.79A. The averaged separations between olefinic carbon(sp^2 hybrid) and chroline are shorter than those between

pyramidal bonding carbon(sp^3 hybrid) and chlorine, the former is 1.724A and the latter is 1.784A. The tendency described above is also shown in the results of HF/STO-3G and HF/6-31G** methods.

Charge Density: Table 2 shows the net atomic charges of carbon and terminal chlorine atoms at the structure calculated by the HF/6-31G** method. MP2/6-31G** results do not cited in the table because they are almost the same as those in Table 2. It can be shown that the electron density on the carbon atoms in HF/6-31G** method are larger than that in HF/STO-3G method. On the other hand the electron density on the terminal chlorine atom in HF/6-31G** method is less than that in HF/STO-3G method. It can be noticed that in the results of HF/STO-3G method the allylic chloropropenes are classified into two groups, one with the positive atomic charge of central carbon atom in C=C-C sequence and another with the negative one. This classification by the sign of the net charge is coincident to the structural characterization whether allylic chloropropenes have chlorine atom at the central carbon atom or not.

Table 2. Net charges of carbon atoms and terminal chlorine atom in HF/6-31G** method[a)]

	Q1	Q2	Q3	Q4
1	-0.271(-0.120)	-0.087(-0.048)	-0.317(-0.058)	-0.104(-0.189)
2	-0.247(-0.110)	-0.104(0.060)	-0.295(-0.058)	-0.071(-0.160)
3 (*cis*)	-0.239(-0.012)	-0.075(-0.039)	-0.330(-0.061)	-0.089(-0.172)
(*trans*)	-0.239(-0.011)	-0.067(-0.039)	-0.324(-0.058)	-0.089(-0.171)
4 (*cis*)	-0.208(0.001)	-0.055(0.061)	-0.319(0.042)	0.012(-0.101)
(*trans*)	-0.221(-0.002)	-0.052(0.059)	-0.312(0.047)	0.012(-0.101)
5 (*cis*)	-0.211(-0.007)	-0.076(0.065)	-0.312(-0.061)	-0.059(-0.147)
(*trans*)	-0.224(-0.009)	-0.073(0.062)	-0.305(-0.057)	-0.062(-0.148)

a) The values in parentheses are net charges in HF/STO-3G method.

Table 3. HOMO and LUMO energies calculated by HF/6-31G** method[a)]

	HOMO	LUMO
1	-0.3804	0.1508
2	-0.3785	0.1530
3 (*cis*)	-0.3773	0.1329
(*trans*)	-0.3758	0.1329
4 (*cis*)	-0.3850	0.1013
(*trans*)	-0.3839	0.1058
5 (*cis*)	-0.3755	0.1115
(*trans*)	-0.3747	0.1162

a) Unit is a.u.

HOMO and LUMO energies: Table 3 shows the HOMO(highest occupied MO) and LUMO (lowest unoccupied MO) energies calculated by HF/6-31G** method. It is found as expected that the number of substituted chlorine is the more the LUMO level becomes the lower.

Protonated allylic chloropropenes: Figure 2 shows the potential energy curves of protonated allylic chloropropenes with respect to the terminal C-Cl distance. At a glance of HF/6-31G** results, it is found that the C-Cl separation lengthens when a proton is added to terminal chlorine atom. This implies that the cleavage of C-Cl bond and the following production of allyl cation and HCl facilitately proceed. While in the HF/STO-3G results the most stable C-Cl separations of protonated 2 and 5 slightly changed from the unprotonated structures.

Discussion

As shown in Table 1 dominant structure in allylic chloropropenes is the conformation 4 with an exception. Most stable geometries of them are also shown to be slightly dependent on the methods of calculation. In the compounds which were determined to be activated through epoxidative pathway by Neudecker and Henschler, the energy differences between conformations 3 and 4, either of which is most stable one, are very small. Especially the second stable conformation 4 in the case of 2 calculated by MP2/6-31G** can not be neglected because the energy increasion from the most stable conformation 3 is only 0.0001a.u.

It is shown from the results in Table 3 that LUMOs in 4 and 5 are lower than those of other compounds. This fact seems to

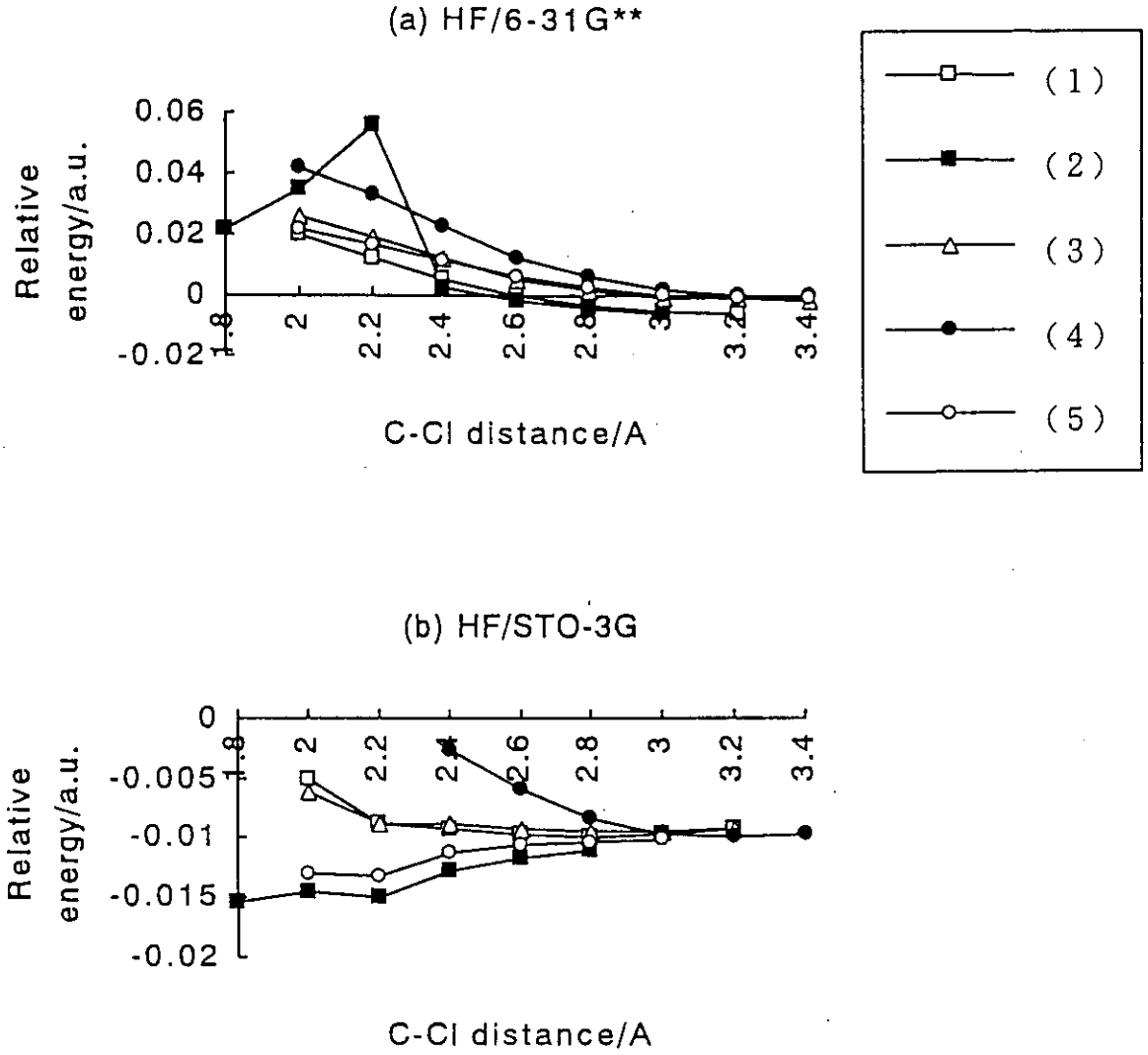


Figure 2. Potential profiles of protonated allylic chloropropenes with respect to C-Cl distance.

indicate the possibility that the lowering of LUMO brings the corresponding epoxide. The LUMO of 2, however, which is classified into epoxidative pathway group, is higher than those of 1 and 3. The disagreement can be detoured by finding the LUMO level of second stable conformation of 2, conformation 4, being rather low, 0.1289a.u. Therefore it can be said that 2, 4 and 5 may be more easily activated through epoxidative pathway than 1 and 3.

Neudecker and Henschler thought that C=C bond in 2, 4 and 5 bears polarization due to *-I* effect of the substitution to chlorine atom at central carbon atom in C=C-C sequence. From the results of HF/6-31G** in Table 2 it can be shown that the net atomic charges of C^1 and C^2 in 2, 4 and 5 are slightly different from those in 1 and 3. In the results of HF/STO-3G method, on the contrary, net charges of central carbon are positive in 2, 4 and 5 while negative in 1 and 3. This fact indicates again that 2, 4 and 5 may be activated through epoxidative pathway more easily than 1 and 3.

It is shown from the HF/STO-3G results in Fugure 2 that the terminal C-Cl

separations of 2 and 5 are slightly affected by protonation to terminal chlorine atom and those in 1, 3 and 4 are lengthened by adding a proton to terminal chlorin atom. If the same situation as this was indicated from the results of other sophisticated procedures, such as HF/6-31G**, it could be concluded that the reactivity of producing allylic cations correlates to the mutagenic potency through hydrolytic-oxidative pathway. But the possibility has to be abandoned due to the results of HF/6-31G** method in Figure 2.

Up to now mutagenic potency through both pathways cloud not be decided clearly from the electronic characteristics of allylic chloropropenes.

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