results show that the experimental data are even slightly better explained by the assumption of an equilibrium between the four conformations A, B, C, and D. However, the alternative of an equilibrium between equal amounts of C and D cannot be excluded experimentally.

In principle, an estimate of the relative populations of the four conformations could be obtained by the calculation of the relative free energies. Different techniques could be used.[27] The configurational entropy of a conformation can be obtained by directly integrating the distribution function, generated by the MD trajectory using harmonic approximation.[28,29] This technique does not allow for incorporation of free energy contributions of the solvent.[27] An alternative is to use umbrella sampling techniques along the pathway leading from one conformation to the other. This method requires a pathway to be postulated but allows the inclusion of solvent contributions to the relative free energy in case a MD simulation in solvent is performed. However, we think that such an approach does not contribute further to the principle of the detection of a conformational equilibrium. Finally, we conclude that when performing conformational analysis on the basis of NMR parameters one must be on the watch for multiple mutually incompatible conformations contributing to the set of NMR parameters. As was shown here, MD simulations may be used to trace such a situation and to get a crude estimate of the conformations involved and their relative populations.

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Theoretical Investigation of the Anaerobic Reduction of Halogenated Alkanes by Cytochrome P-450. 2. Vertical Electron Affinities of Chlorofluoromethanes as a Measure of Their Activity

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Abstract: The electron-accepting ability of chlorofluoromethanes is determined by both ab initio and MNDO methods. For the full set of molecules (CH_3F, CH_2F_2, CHF_3, CF_4, CH_3Cl, CH_2Cl_2, $CHCl_3$, CCl_4, CH_2FCl, CHF_2Cl, $CHFCl_2$, CF_3Cl, CF_2Cl_2, $CFCl_3$), the vertical electron affinity (VEA) is calculated. The VEA is defined as the negative of the energy change on going from the neutral molecule, at its equilibrium geometry, to the metastable anion, leading to dissociative electron attachment, at the same geometry. The geometry of the neutral molecule is totally optimized at the ab initio and MNDO levels. The ab initio optimization uses 3-21G and 6-31G* basis sets. Single-point calculations are performed at the HF/3-21G optimized geometry on a 6-31G* basis with second-order Moller-Plesset perturbation theory. A direct correlation is found between the VEA of a compound and its activity toward reductive metabolism. Of the nine species that have been experimentally examined, these results correctly predict their relative activity and allow a prediction of the activity of the remaining five compounds.

Several halogenated hydrocarbons are known to be reductively dehalogenated by cytochrome P-450 under anaerobic conditions.[1] As discussed in the first paper of this series, hereafter referred to as I,[2] the first step in this process is the binding of the halocarbon to the enzyme (Figure 1 in I). While large halogenated hydrocarbons are known to act as "type I" substrates binding to a hydrophobic site of the enzyme that is near, but not attached to, the heme unit, halomethanes may loosely interact with the iron. Evidence for this comes from the recent observation that the binding of camphor to the hydrophobic site of $P\text{-}450_{cam}$ from *Pseudomonas putida* does not affect the rate of reductive dehalogenation of CCl_4 and $BrCCl_3$.[3] Wade and Castro have proposed that CH_3I can form a loose affiliation with the iron, producing a change in the heme visible spectrum but no change in the NMR spectrum.[4]

Under reducing conditions, and in the absence of molecular oxygen, an electron can be transferred from the enzyme to the substrate. It has been suggested that the concentration of O_2 may be quite low in the center of liver lobules.[5] This reduced halocarbon dissociates to a halide anion and a haloalkyl radical. The radical can, after a second reductive dehalogenation, form an iron-carbene complex or leave the enzyme and abstract a lipid hydrogen, initiating lipid peroxidation and tissue damage. It may also directly inactivate the enyzyme through further reactions, though the mechanism for this is not well understood.[6]

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Evidence that a halomethane undergoes anaerobic reduction is usually obtained by monitoring the Soret band in the difference spectra. Formation of a carbene–cytochrome P-450 complex leads to a Soret absorption band in the 450–470-nm range in the difference spectrum. Such spectral shifts have been observed for seven halomethanes (CCl_4,[7-11] $CFCl_3$,[7,9,12] CCl_3Br,[7] CBr_4,[7] $CHBr_3$,[7,13] CHI_3,[7] $CHCl_3$[7]) although the spectrum of $CHCl_3$ forms very slowly.

In addition to spectral changes during CCl_4 metabolism, direct evidence for the formation of a dichlorocarbene comes from the observation of 1,1-dichloro-2,2,3,3-tetramethylcyclopropane, which is thought to arise from a reaction between the carbene and 2,3-dimethyl-2-butene.[14]

With $CHCl_3$, there is disagreement as to whether it is reductively dehalogenated[15,16] and whether it causes lipid peroxidation.[17,18] The fact that a carbene peak in the Soret band of the difference spectrum forms very slowly[7] suggests that chloroform is a substrate for reductive dehalogenation, but this occurs slowly and is totally stopped if any molecular oxygen is present. Without molecular oxygen, a (halomethyl)peroxy radical cannot be formed,[19] greatly reducing the peroxidation potency. This is in agreement with the observation that chloroform is not metabolized to an electrophilic form of chlorine.[15]

Among the dihalomethanes, only a spectral shift from CH_2Br_2 has been reported, but it too is controversial and has not been obtained for other dihalomethanes.[7,20]

It should be stressed that the formation of a carbene peak in the difference spectrum requires the halomethane to be reductively dehalogenated twice. The production of a halomethyl radical, which can initate tissue damage, requires only a single reductive dehalogenation. If the potential leading to reductive dehalogenation of a halomethane is high, dissociative electron attachment may occur, producing the halomethyl radical. If the dissociative reduction potential of the resulting radical is low, it will probably not be further reduced to the carbene but may still initiate lipid peroxidation. Therefore, compounds that do not produce the carbene–cytochrome P-450 complex may still be able to form the halomethyl radical and cause tissue damage.

There seems to be a good correlation between the rate of reductive metabolism and the ease of electrochemical reduction of the carbon–halogen bond, which is known to decrease in the order I, Br, Cl, F.[21] This has led to the conclusion that the reduction potential of a halogenated compound is an important determinant of whether reductive metabolism will occur.[22] Assuming that the abstraction of an electron from reduced cytochrome P-450 is the rate-limiting step, any molecule with a reduction potential greater than that of $CHCl_3$ should be a substrate of reductive metabolism; one with a reduction potential less than that of $CHCl_3$ will not. Since there is at most only a weak affiliation between the halomethane and the heme, we will assume that the structure of the halomethane is the same as that in the gas phase. We will also assume that the electron transfer from the enzyme to the substrate occurs fast enough to preclude a change in the geometry of the halocarbon as it accepts the electron. This makes the interaction of a free electron with the halocarbon a reasonable model system.

The theoretical calculations presented here measure the energy difference between the halomethane and the metastable state of the anion leading to halide dissociation, both at the equilibrium geometry of the neutral molecule. The reaction under investigation is eq 1, where CY_3X represents a general halomethane. The

$$CY_3X + e^- \rightarrow CY_3X^- \quad (1)$$

negative of the enthalpy change for reaction 1 is the vertical electron affinity (VEA) for this species. The molecules examined in this study are all possible chlorofluoromethanes (CH_3F, CH_2F_2, CHF_3, CF_4, CH_3Cl, CH_2Cl_2, $CHCl_3$, CCl_4, CH_2FCl, CHF_2Cl, $CHFCl_2$, CF_3Cl, CF_2Cl_2, $CFCl_3$). The VEA for each is calculated by both ab initio and MNDO methods. Since the eventual goal is to extend these calculations to bromo- and iodomethanes[23] and -ethanes, ab initio methods cannot be exclusively used since the size of these systems currently precludes our use of all-electron calculations. Of the 14 molecules treated here, 9 have been examined experimentally and serve as a check of the assumptions made above.

Methods of Calculation

An experimentally observed resonance state leading to dissociative electron attachment can be described as a localized continuum wave function that resembles a bound state for a time $1/T$, where T is the width of the resonance.[24] This metastable resonance state has been associated with the addition of an electron to a carbon–halogen antibonding orbital.[25,26] If we neglect any electron relaxation within the neutral molecule upon addition of the extra electron, the energy separation between the vertical anion and neutral molecule can be approximated by the orbital energy of the carbon–halogen antibonding orbital. Virtual orbital energies have been used to aid in the assignment of resonances observed in electron transmission spectroscopy.[26] If a valence-only basis set is used to calculate the orbital energies in halomethanes, the lowest unoccupied molecular orbital (LUMO) will correspond to the energetically most accessible carbon–halogen antibonding orbital. Within this basis, an SCF calculation of the vertical anion would yield a reasonable description of the lowest energy dissociative electron attachment resonance state. If diffuse functions are included in the basis set, the LUMO will be a diffuse orbital, not the carbon–halogen antibonding orbital. An SCF calculation of the vertical anion with this basis would yield a state that does not correspond to a dissociative electron attachment resonance. This change in character of the LUMO is why a previous theoretical study has shown a correlation between the energy of the LUMO and the VEA if a 3-21G or 6-31G* basis is used but not with a 6-31+G* basis, which includes diffuse functions on all non-hydrogen atoms.[27]

By both MNDO[28] and ab initio[29] methods, the geometry of each neutral chlorofluoromethane is totally optimized. For the ab initio calculations, the split-valence 3-21G[30] and 6-31G*[31] basis sets are used. The latter basis includes polarization functions on all non-hydrogen atoms. The MNDO-, HF/3-21G-, and HF/6-31G*-optimized geometries are presented in Table I, along with the experimental structures. The energy of the neutral molecule is determined by restricted Hartree–Fock theory[32] (RHF); unrestricted Hartree–Fock[33] (UHF) formalism is used for the

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Table I. MNDO, HF/3-21G, HF/6-31G*, and Experimental Geometries of F- and Cl- Substituted Methanes[a]

molecule	parameter	MNDO	HF/ 3-21G	HF/ 6-31G*	expt
CH_3F	R(C-F)	1.347	1.404	1.365	1.383[b]
	R(C-H)	1.118	1.080	1.082	1.100
	A(H-C-F)	110.6	109.4	109.1	108.3
CH_2F_2	R(C-F)	1.352	1.372	1.338	1.357[c]
	R(C-H)	1.129	1.073	1.078	1.093
	A(F-C-X)	53.4	54.4	54.3	54.2
	A(H-C-X)	125.9	124.1	123.8	123.2
CHF_3	R(C-H)	1.136	1.066	1.074	1.098[d]
	R(C-F)	1.353	1.345	1.317	1.332
	A(F-C-H)	111.5	110.6	110.4	110.1
CF_4	R(C-F)	1.347	1.325	1.302	1.320[e]
CH_3Cl	R(C-Cl)	1.795	1.892	1.785	1.778[f]
	R(C-H)	1.102	1.074	1.078	1.086
	A(H-C-Cl)	108.1	106.2	108.4	108.2
CH_2Cl_2	R(C-Cl)	1.786	1.853	1.768	1.772[g]
	R(C-H)	1.103	1.069	1.074	1.068
	A(Cl-C-X)	55.6	55.4	55.5	55.9
	A(H-C-X)	123.8	122.8	124.5	124.0
$CHCl_3$	R(C-H)	1.105	1.067	1.071	1.100[h]
	R(C-Cl)	1.782	1.835	1.763	1.758
	A(Cl-C-H)	108.6	108.4	107.6	107.6
CCl_4	R(C-Cl)	1.782	1.832	1.766	1.760[i]
CH_2FCl	R(C-H)	1.116	1.069	1.076	1.078[j]
	R(C-F)	1.336	1.369	1.341	1.378
	R(C-Cl)	1.822	1.886	1.772	1.759
	A(H-C-X)	55.4	60.7	56.0	56.0
	A(F-C-X)	130.3	131.9	126.5	124.2
	A(Cl-C-X)	118.6	123.0	123.6	125.8
CHF_2Cl	R(C-F)	1.342	1.345	1.320	1.350[k]
	R(C-H)	1.126	1.065	1.073	1.090
	R(C-Cl)	1.839	1.867	1.758	1.740
	A(F-C-X)	53.6	54.9	54.2	53.5
	A(H-C-X)	129.7	130.4	125.9	127.7
	A(Cl-C-X)	125.5	123.1	124.8	125.3
$CHFCl_2$	R(C-Cl)	1.811	1.845	1.758	1.750[l]
	R(C-F)	1.330	1.353	1.329	1.367
	R(C-H)	1.116	1.066	1.072	1.090
	A(Cl-C-X)	54.2	55.1	56.0	56.1
	A(F-C-X)	127.6	124.7	125.8	125.7
	A(H-C-X)	119.8	122.9	124.7	127.3
CF_3Cl	R(C-Cl)	1.838	1.833	1.747	1.751[m]
	R(C-F)	1.344	1.329	1.306	1.328
	A(F-C-Cl)	110.5	109.4	110.3	110.3
CF_2Cl_2	R(C-Cl)	1.825	1.836	1.752	1.744[n]
	R(C-F)	1.337	1.335	1.313	1.345
	A(Cl-C-X)	53.4	55.3	56.1	56.3
	A(F-C-X)	126.2	125.0	126.1	126.9
$CFCl_3$	R(C-F)	1.327	1.347	1.322	1.330[o]
	R(C-Cl)	1.806	1.833	1.758	1.760
	A(Cl-C-F)	110.8	108.6	108.0	109.5

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vertical anion. To determine the effect of partial electron correlation, single-point calculations are performed on the 6-31G* basis set and second-order Moller–Plesset perturbation theory[34] with HF/3-21G-optimized structures. These calculations will be denoted MP2/6-31G*//HF/3-21G, where the level of theory used to calculate the energy is given to the left of the // and the level used to optimize the geometry is given to the right. The energies of the parent molecules and vertical anions are presented in Table II.

Table II. MNDO, HF/3-21G, MP2/6-31G*//HF/3-21G, and HF/6-31G* Energies for the F- and Cl-Substituted Methanes, Their Vertical Anions, and the Dissociation Products[a]

molecule	MNDO	HF/3-21G	MP2/6-31G*	HF/6-31G*
CH_3F	−60.9	−138.281 89	−139.335 44	−139.034 62
CH_2F_2	−111.8	−236.609 10	−238.363 52	−237.896 35
CHF_3	−163.8	−334.951 73	−337.406 73	−336.771 64
CF_4	−214.2	−433.296 32	−436.447 41	−435.645 21
CH_3Cl	−22.0	−496.689 48	−499.349 94	−499.093 15
CH_2Cl_2	−27.1	−953.390 60	−958.369 98	−957.985 18
$CHCl_3$	−27.6	−1410.084 22	−1417.387 59	−1416.869 71
CCl_4	−23.6	−1866.771 86	−1876.399 73	−1875.744 84
CH_2FCl	−67.5	−594.993 76	−598.361 02	−597.936 72
CHF_2Cl	−114.0	−693.315 17	−697.389 62	−696.796 90
$CHFCl_2$	−68.3	−1051.691 73	−1057.385 32	−1056.829 29
CF_3Cl	−159.2	−791.645 32	−796.428 71	−795.663 20
CF_2Cl_2	−109.3	−1150.006 68	−1156.413 11	−1155.684 68
$CFCl_3$	−63.9	−1508.381 68	−1516.403 25	−1515.711 64
CH_3F^-	14.7	−138.018 28	−139.110 07	−138.797 01
$CH_2F_2^-$	−46.5	−236.349 99	−238.133 72	−237.657 91
CHF_3^-	−127.7	−334.690 53	−337.164 36	−336.526 76
CF_4^-	−181.9	−432.920 20	−436.114 05	−435.237 28
CH_3Cl^-	−5.5	−496.563 21	−499.229 16	−498.930 24
$CH_2Cl_2^-$	−34.8	−953.312 81	−958.289 81	−957.866 63
$CHCl_3^-$	−55.3	−1410.045 48	−1417.344 43	−1416.778 86
CCl_4^-	−67.0	−1866.761 69	−1876.390 46	−1875.682 38
CH_2FCl^-	−69.3	−594.882 86	−598.247 51	−597.781 49
CHF_2Cl^-	−134.2	−693.215 67	−697.281 62	−696.649 59
$CHFCl_2^-$	−94.8	−1051.633 07	−1057.315 94	−1056.721 22
CF_3Cl^-	−201.2	−791.555 45	−796.322 65	−795.527 40
$CF_2Cl_2^-$	−157.3	−1149.967 47	−1156.355 90	−1155.589 96
$CFCl_3^-$	−111.5	−1508.367 84	−1516.376 30	−1515.641 57
CH_3	24.6	−39.342 61	−39.668 64	−39.558 99
CH_2F	−34.4	−137.652 64	−138.678 75	−138.402 11
CHF_2	−89.5	−235.979 24	−237.707 96	−237.263 13
CF_3	−138.7	−334.313 36	−336.744 01	−336.131 18
CH_2Cl	11.4	−496.052 51	−498.691 96	−498.461 08
$CHCl_2$	3.0	−952.754 01	−957.717 42	−957.358 05
CCl_3	−0.6	−1409.450 42	−1416.740 22	−1416.248 16
$CHFCl$	−41.7	−594.360 07	−597.707 20	−597.306 23
CF_2Cl	−90.1	−692.680 45	−696.735 39	−696.163 29
$CFCl_2$	−43.2	−1051.058 11	−1056.733 53	−1056.201 59
F^-	−17.1	−98.772 14	−99.526 61	−99.350 28
Cl^-	−54.2	−457.353 59	−459.652 10	−459.526 00

[a] MNDO heats of formation are in kilocalories/mole; all other energies are in hartrees.

Table III. MNDO, HF/3-21G, and HF/6-31G* Average Absolute Errors in the Geometries of F- and Cl-Substituted Methanes[a]

parameter	MNDO	HF/3-21G	HF/6-31G*
R(C-H)	0.028	0.020	0.015
R(C-F)	0.020	0.011	0.024
R(C-Cl)	0.051	0.094	0.008
angles	1.971	1.895	0.748

[a] Errors are in angstroms for bond lengths and degrees for bond angles.

Examination of reaction 1 shows that the energy of the reactant will be calculated by RHF theory while the products will use RHF and UHF theory. This change between RHF and UHF leads to an unbalancing of the reaction energy, similar to the "nonisogyric problem" encountered in the theoretical calculation of the total atomization energy and heat of formation of simple molecules.[35] For reaction 2, where CY_3 is the

$$CY_3 + X^- \rightarrow CY_3X^- \qquad (2)$$

(34) Binkley, J. S.; Pople, J. A. *Int. J. Quantum Chem.* **1975**, *9*, 229.
(35) Pople, J. A.; Frisch, M. J.; Luke, B. T.; Binkley, J. S. *Int. J. Quantum Chem. Symp.* **1983**, *17*, 307. Pople, J. A.; Luke, M. J.; Frisch, M. J.; Binkley, J. S. *J. Phys. Chem.* **1985**, *89*, 2198. Luke, B. T.; McLean, A. D. *J. Phys. Chem.* **1985**, *89*, 4592.

Table IV. MNDO, HF/3-21G//HF/3-21G, MP2/6-21G*//HF/3-21G, and HF/6-31G*//HF/6-31G* Energies of Reaction 2 (kcal/mol)

CY_3	X^-	MNDO	HF/ 3-21G	MP2/ 6-31G*	HF/ 6-31G*
CH_3	F^-	7.2	60.5	53.5	70.4
CH_2F	F^-	5.0	46.9	45.0	59.3
CHF_2	F^-	-21.1	38.2	44.1	54.4
CF_3	F^-	-26.1	103.7	98.2	153.2
CH_3	Cl^-	24.1	83.5	57.5	97.1
CH_2Cl	Cl^-	8.0	58.5	34.0	75.6
$CHCl_2$	Cl^-	-4.1	39.0	15.7	66.0
CCl_3	Cl^-	-12.2	26.6	1.2	57.6
CH_2Cl	F^-	-63.6	-36.5	-18.2	18.7
CH_2F	Cl^-	19.3	77.4	52.3	92.0
CHFCl	F^-	-75.4	-52.4	-30.0	4.3
CHF_2	Cl^-	9.5	73.5	49.2	87.6
$CHCl_2$	F^-	-80.7	-67.1	-45.1	-8.1
CHFCl	Cl^-	1.1	50.6	27.2	69.7
CF_2Cl	F^-	-94.0	-64.5	-38.1	-8.7
CF_3	Cl^-	-8.3	70.0	46.1	81.4
$CFCl_2$	F^-	-97.0	-86.1	-60.1	-23.9
CF_2Cl	Cl^-	-13.0	41.8	19.8	62.3
CCl_3	F^-	-93.8	-91.2	-68.7	-27.1
$CFCl_2$	Cl^-	-14.1	27.5	5.9	54.0

halomethyl radical and X^- is the halide anion, UHF calculations are needed for both a reactant and the product. This balances the method of calculation and should yield a more accurate value. If this reaction is coupled with eq 3, the sum yields reaction 1. The heat of reaction for

$$CY_3X + e^- \rightarrow CY_3 + X^- \quad (3)$$

(3) can be determined from the MP2/6-31G*//HF/3-21G heats of formation presented in Table XIII of I and the known heats of formation of F^- and Cl^-.[36] Therefore, the MNDO, HF/3-21G//HF/3-21G, HF/6-31G*//HF/6-31G*, and MP2/6-31G*//HF/3-21G results will be presented in two different forms; the VEA obtained from the calculated energy change of reaction 1, denoted VEA1, and the VEA values determined from the energy change of reaction 2, presented in Table IV, and the enthalpy change of reaction 3, denoted VEA2. This calculated value is unbalanced since the heats of formation presented in I were generated from reactions that used scaled HF/3-21G frequencies. Therefore, zero-point vibrational energies are included in reaction 3, while only the calculated energies in Table II are used to determine the energy change of reaction 2. Table IV shows that the vertical anion is unstable with respect to the lowest energy dissociation product at all ab initio levels, so the vibrational energy contribution to reaction 2 is expected to be small and totally masked by the uncertainty in the heats of formation listed in Table XIII of I.

Results

A comparison of the experimental and theoretical geometries is presented in Table III. This table gives the average absolute errors in the calculated bond lengths and angles. In general, the C–F bond lengths are in better agreement with experiment at the HF/3-21G level; the HF/6-31G* results are in better agreement for all other values. It is interesting to note that the HF/3-21G results predict C–Cl bond lengths that are substantially longer than experiment, with the HF/6-31G* structures giving very good values. Longer C–Cl bond lengths at the HF/3-21G level were also found in the chlorinated methyl radicals discussed in I.

Calculations of the energy change for reaction 2 (Table IV) show that at the HF/6-31G* level the vertical anions are less stable compared to the dissociation products than at the HF/3-21G level. Inclusion of electron correlation (MP2/6-31G*//HF/3-21G) stabilizes the vertical anions with respect to dissociation. The HF/3-21G, HF/6-31G*, and MP2/6-31G*//HF/3-21G calculations all predict that the vertical anions are unstable with respect to dissociation for both the fluoro- and chloromethanes. They also show that the chlorofluoromethane vertical anions are generally unstable relative to dissociation of a chloride anion and stable with respect to a fluoride anion. The MNDO calculations predict that CHF_3^-, CF_4^-, $CHCl_3^-$, CCl_4^-, CF_3Cl^-, $CF_2Cl_2^-$, and $CFCl_3^-$ are stable relative to the lowest energy dissociation product.

When the data in Table IV are used to calculate VEA2, it is assumed that the methods are able to treat the fluoride and chloride anions with equal accuracy. There is no reason to assume this, so we have determined the values of VEA2 for the chlorofluoromethanes using both F^- and Cl^- as X^- in reactions 2 and 3. If the methods employed here treat these anions equally, the two values of VEA2 should be the same for each chlorofluoromethane. The difference in the VEA2 values for each molecule is listed in Table V. The major source of this difference appears to be the relative accuracy in describing F^- and Cl^- since the change in VEA2 values is relatively constant for this set of molecules. Also, the average of these differences is very close to the error in the electron affinity difference between atomic fluorine and chlorine. The energy change for the reaction

$$F + Cl^- \rightarrow F^- + Cl$$

can be compared to the difference in experimental electron affinities of fluorine and chlorine[36] and is found to be in error by 47.2, 90.5, 34.3, and 54.6 kcal/mol at the MNDO, HF/3-21G, MP2/6-31G*, and HF/6-31G* levels, respectively. Therefore, the average difference will be added to the VEA2 values for all

Table V. Difference in the Calculated Values of VEA2 for F^- and Cl^- Used as X^- in Reactions 2 and 3 (kcal/mol)

CY_3X	MNDO	HF/3-21G	MP2/6-31G*	HF/6-31G*
CH_2FCl	54.6	85.6	42.2	45.0
CHF_2Cl	47.9	88.9	42.2	47.3
$CHFCl_2$	51.6	87.5	42.1	47.6
CF_3Cl	43.9	92.7	42.4	48.3
CF_2Cl_2	46.2	90.1	42.1	48.4
$CFCl_3$	45.5	84.5	40.4	46.9
av	48.3	88.2	41.9	47.2

Table VI. MNDO, HF/3-21G//HF/3-21G, MP2/6-31G*//HF/3-21G, and HF/6-31G*//HF/6-31G* Values of VEA1 (eV)

MNDO	HF/3-21G	MP2/6-31G*	HF/6-31G*
CF_2Cl_2 (2.08)	CCl_4 (-0.28)	CCl_4 (-0.25)	CCl_4 (-1.70)
$CFCl_3$ (2.06)	$CFCl_3$ (-0.38)	$CFCl_3$ (-0.73)	$CFCl_3$ (-1.91)
CCl_4 (1.88)	$CHCl_3$ (-1.05)	$CHCl_3$ (-1.17)	$CHCl_3$ (-2.47)
CF_3Cl (1.82)	CF_2Cl_2 (-1.07)	CF_2Cl_2 (-1.56)	CF_2Cl_2 (-2.58)
$CHCl_3$ (1.20)	$CHFCl_2$ (-1.60)	$CHFCl_2$ (-1.89)	$CHFCl_2$ (-2.94)
$CHFCl_2$ (1.15)	CH_2Cl_2 (-2.12)	CH_2Cl_2 (-2.18)	CH_2Cl_2 (-3.23)
CHF_2Cl (0.88)	CF_3Cl (-2.45)	CF_3Cl (-2.89)	CF_3Cl (-3.70)
CH_2Cl_2 (0.33)	CHF_2Cl (-2.71)	CHF_2Cl (-2.94)	CHF_2Cl (-4.01)
CH_2FCl (0.08)	CH_2FCl (-3.02)	CH_2FCl (-3.09)	CH_2FCl (-4.22)
CH_3Cl (-0.72)	CH_3Cl (-3.44)	CH_3Cl (-3.29)	CH_3Cl (-4.43)
CF_4 (-1.40)	CH_2F_2 (-7.05)	CH_3F (-6.13)	CH_3F (-6.47)
CHF_3 (-1.57)	CHF_3 (-7.11)	CH_2F_2 (-6.25)	CH_2F_2 (-6.49)
CH_2F_2 (-2.83)	CH_3F (-7.17)	CHF_3 (-6.60)	CHF_3 (-6.66)
CH_3F (-3.28)	CF_4 (-10.23)	CF_4 (-9.07)	CF_4 (-11.10)

Table VII. MNDO, HF/3-21G//HF/3-21G, MP2/6-31G*//HF/3-21G, and HF/6-31G*//HF/6-31G* Values of VEA2 (eV)

MNDO	HF/3-21G	MP2/6-31G*	HF/6-31G*
CCl_4 (0.87)	CCl_4 (-0.87)	CCl_4 (0.29)	CCl_4 (-2.16)
$CFCl_3$ (0.74)	$CFCl_3$ (-1.07)	$CFCl_3$ (-0.13)	$CFCl_3$ (-2.22)
CF_2Cl_2 (0.47)	$CHCl_3$ (-1.49)	$CHCl_3$ (-0.48)	$CHCl_3$ (-2.66)
$CHCl_3$ (0.38)	CF_2Cl_2 (-1.91)	CF_2Cl_2 (-0.95)	CF_2Cl_2 (-2.80)
CF_3Cl (0.06)	$CHFCl_2$ (-2.23)	$CHFCl_2$ (-1.21)	$CHFCl_2$ (-3.06)
$CHFCl_2$ (-0.08)	CH_2Cl_2 (-2.44)	CH_2Cl_2 (-1.38)	CH_2Cl_2 (-3.18)
CH_2Cl_2 (-0.25)	CF_3Cl (-3.33)	CF_3Cl (-2.30)	CF_3Cl (-3.83)
CHF_2Cl (-0.58)	CHF_2Cl (-3.36)	CHF_2Cl (-2.31)	CHF_2Cl (-3.97)
CH_2FCl (-0.88)	CH_2FCl (-3.39)	CH_2FCl (-2.31)	CH_2FCl (-4.03)
CH_3Cl (-0.94)	CH_3Cl (-3.52)	CH_3Cl (-2.39)	CH_3Cl (-4.08)
CF_4 (-3.36)	CH_3F (-7.56)	CH_3F (-5.25)	CH_3F (-6.21)
CHF_3 (-3.38)	CH_2F_2 (-7.57)	CH_2F_2 (-5.48)	CH_2F_2 (-6.33)
CH_3F (-3.52)	CHF_3 (-7.68)	CHF_3 (-5.93)	CHF_3 (-6.61)
CH_2F_2 (-4.02)	CF_4 (-10.72)	CF_4 (-8.47)	CF_4 (-11.08)

(36) From the known electron affinities of F and Cl (79.6 and 83.2 kcal/mol, respectively) and the heat of formation of F (18.86 kcal/mol; Stull, D. R., Prophet, H., Project Directors *JANAF Thermochemical Tables*, 2nd ed.; NSRDS-NBS 37; U.S. Government Printing Office: Washington, DC, 1971) and Cl (28.99 kcal/mol; Chase, M. W.; Curnutt, J. L.; Hu, A. T.; Porphet, H.; Syverud, A. N.; Walker, L. C. *J. Phys. Chem. Ref. Data* **1974**, *3*, 311.).

Table VIII. Results of a Linear Fit of the VEA Values to E(LUMO), Including the Fitting Parameters (A and B), the Average Absolute Error (AAE), and the Maximum Absolute Error (MAE)

parameter	MNDO	HF/3-21G// HF/3-21G	HF/6-31G*// HF/6-31G*
		VEA1	
A[a]	−1.079	−29.115	−28.461
B[b]	0.296	1.307	1.103
AAE[b]	0.109	0.156	0.169
MAE[b]	0.33	0.37	0.44
		VEA2	
A[a]	−0.982	−28.666	−27.121
B[b]	−0.875	0.704	0.821
AAE[b]	0.520	0.222	0.198
MAE[b]	0.92	0.54	0.43

[a] In units of electron volts/hartree. [b] In units of electron volts.

fluoromethanes, and only the reactions producing Cl^- will be used to the other compounds.

The resulting values of VEA1 and VEA2 for each molecule are presented in Tables VI and VII, respectively. For each computational method, the chlorofluoromethanes are listed from best to worst electron acceptor. A comparison of these tables shows that virtually the same ordering of electron-accepting ability is obtained from both VEA1 and VEA2 when ab initio methods are used. There is also excellent agreement between the HF/3-21G, MP2/6-31G*//HF/3-21G, and HF/6-31G* orderings. The MNDO results also agree with this ordering when VEA2 values are used; the agreement with VEA1 values is not as good.

Discussion

From the results in Table VI and VII, CCl_4 and $CFCl_3$ are predicted to be better electron acceptors than $CHCl_3$ and should be substrates for reductive metabolism by cytochrome P-450. Experimentally, these compounds are known to be active substrates. Six compounds (CH_3F, CH_2F_2, CHF_3, CF_4, CH_3Cl, CH_2Cl_2) are experimentally known to be inactive as substrates. The results in Tables VI and VII agree with these observations since the compounds are found to be poorer electron acceptors than chloroform. In addition, we predict that four other compounds (CH_2FCl, CHF_2Cl, CF_3Cl, $CHFCl_2$) should be inactive as substrates, though no experimental work on these molecules is known.

The remaining halomethane, CF_2Cl_2, has an electron-accepting ability that is quite close to that of $CHCl_3$, suggesting that it may be marginally active. For example, the difference in VEA2 values between $CHCl_3$ and CF_2Cl_2 is only 0.14 eV (3.2 kcal/mol) at the HF/6-31G*//HF/6-31G* level. The errors in the heats of formation used to calculate the enthalpy change of reaction 3 (Table XIII of I) and any uncertainties in the calculated energy of reaction 2 produce an uncertainty in VEA2 that is larger than this difference. CF_2Cl_2 has not been experimentally examined and is the only unstudied molecule that may be a substrate for reductive metabolism.

Heinrich and co-workers have found a correlation between the experimental VEA and the value of E(LUMO) determined from HF/3-21G//HF/3-21G and HF/6-31G*//HF/6-31G* calculations.[27] They observed that, for similar compounds, the VEA linearly depends on E(LUMO). We therefore fit a function of the form

$$\text{VEA} = A^*E(\text{LUMO}) + B$$

to the calculated VEA values at the MNDO, HF/3-21G// HF/3-21G, and HF/6-31G*//HF/6-31G* levels. The resulting values of A and B are listed in Table VIII for fits to both VEA1 and VEA2. In addition, the average absolute error between the line and the calculated VEA values for the 14 molecules and the maximum absolute error is given. It can be seen that there is a better fit with VEA1 than VEA2 values for each computational method. We can therefore conclude that the values of E(LUMO) may be used as a measure of the VEA for haloalkanes only for those methods that have reliable relative values of VEA1. This precludes using E(LUMO) for the MNDO method.

Table IX. Comparison of Experimental and Calculated Vertical Electron Affinities (eV) with All Calculated Values Shifted To Match with Experiment for $CHCl_3$

molecule	expt	MNDO	HF/ 3-21G// HF/3-21G	MP2/ 6-31G*// HF/3-21G	HF/ 6-31G*// HF/6-31G*
			VEA1		
CH_3Cl	−3.48	−2.27	−2.74	−2.47	−2.31
CH_2Cl_2	−1.23	−1.22	−1.42	−1.36	−1.11
$CHCl_3$	−0.35	−0.35	−0.35	−0.35	−0.35
$CHFCl_2$	−0.96	−0.40	−0.90	−1.07	−0.82
CF_2Cl_2	−0.98	0.53	−0.37	−0.74	−0.46
			VEA2		
CH_3Cl	−3.48	−1.67	−2.38	−2.26	−1.77
CH_2Cl_2	−1.23	−0.98	−1.30	−1.25	−0.87
$CHCl_3$	−0.35	−0.35	−0.35	−0.35	−0.35
$CHFCl_2$	−0.96	−0.81	−1.09	−1.08	−0.75
CF_2Cl_2	−0.98	−0.26	−0.77	−0.82	−0.49

E(LUMO)

molecule	expt	MNDO	HF/3-21G	HF/6-31G*
CH_3Cl	−3.48	−2.03	−0.43	−0.42
CH_2Cl_2	−1.23	−1.11	−0.39	−0.38
$CHCl_3$	−0.35	−0.35	−0.35	−0.35
$CHFCl_2$	−0.96	−0.25	−0.37	−0.37
CF_2Cl_2	−0.98	0.71	−0.35	−0.36

A comparison between the experimental[26] and calculated VEA values of the five chlorofluoromethanes that have been studied is presented in Table IX. In this table, all calculated VEA values have been shifted to the experimental value of −0.35 eV for $CHCl_3$. Also included in this table are the MNDO, HF/3-21G, and HF/6-31G* values of E(LUMO), which have also been shifted to match the experimental VEA of $CHCl_3$. The shifted VEA values at HF/3-21G, MP2/6-31G*//HF/3-21G, and HF/6-31G* levels are in good agreement with experiment for CH_2Cl_2 and $CHFCl_2$ using either VEA1 or VEA2 values. The MNDO VEA2 values also show reasonable agreement for these molecules. No method of calculation is able to give a good VEA for CH_3Cl, while the MP2/6-31G*//HF/3-21G VEA2 value is in reasonable agreement with experiment for CF_2Cl_2. It should be stressed that these calculations will only yield accurate values of the VEA when the width of the resonance is very narrow. In this case, the resonance state will have significant bound-state character, without a large contribution from the continuum wave functions. It is clear that this is not the case for CH_3Cl and to some extent for CF_2Cl_2. Table IX does show that the method presented here gives VEA values that are much better than that obtained from E-(LUMO), but even better values will have to be obtained by a computational method that includes the effects of the continuum wave functions. Even with the inherent error in calculating VEA values, the method presented here is a useful means of determining which halogenated hydrocarbons will be substrates for reductive dehalogenation by cytochrome P-450.

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