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Quantum Chemical and Statistical Thermodynamic Investigations of Anesthetic Activity. 2. The Interaction between Chloroform, Fluoroform, and a N—H···O=C Hydrogen Bond

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Abstract: Hydrogen bonds of the N—H···O=C type are essential for shaping proteins and therefore determining the structure and dimensions of ion channels in nerve cell membranes. Since it has been postulated that molecules having anesthetic potency are able to perturb hydrogen bonds and that this is a factor in the mechanism of anesthesia, the interaction of a hydrogen bond of this type with chloroform (a potent anesthetic) and fluoroform (no anesthetic potency) has been investigated by quantum chemical and statistical thermodynamic means. The results show that chloroform favors the dissociation of the N—H···O=C hydrogen bond in the formamide dimer, used as a model system, and the formation of a formamide–chloroform dimer instead.

The proper functioning of the nervous system is conditioned by the permeability of the nerve cell membrane to ions which, in turn, depends on the structure and dimensions of the ion channels. The latter is determined by the conformation of the macromolecules (lipids and proteins) which form the membrane. These depend, among other factors, on a number of weak interactions, van der Waals interactions, both polar and nonpolar, and hydrogen bonds. All available evidence indicates that anesthesia is caused by the reversible perturbation of some of these interactions. In our laboratory the possible role of hydrogen bonds have been investigated by means of vibrational spectroscopy and, in a preceding paper[4] (henceforth referred to as paper 1), by means of quantum chemical and statistical thermodynamic calculations. In paper 1 we have investigated the action of chloroform (a potent anesthetic), cyclopropane (a weaker anesthetic), and fluoroform (no anesthetic potency) on the single hydrogen bond in a water dimer. Hydrogen bonds of this type occur in the cell membrane. In the present paper this investigation is extended to the N—H···O=C hydrogen bond which is of vital importance for determining the structure of peptides and proteins. Our model has been the dimer of formamide against chloroform or fluoroform.

References to previous work and general references on anesthesia were given in paper 1.

Outline of the Work

The ability of a compound A to "break" the H bond in the formamide dimer (equilibrium 1) can be determined from the equilibrium constant K_T. The K_T can be calculated from relation

$$H_2NCHO \cdots HNHCHO + A \overset{K_T}{\rightleftharpoons} H_2NCHO \cdots A + H_2NCHO \quad (1)$$

2, using the change of the Gibbs free energy, $\Delta G°$. Let us briefly

$$\Delta G°_T = -RT \ln K_T \quad (2)$$

recapitulate the strategy of the calculations. In order to determine theoretically $\Delta G°_T$ it is necessary to know the following for all systems in equilibrium 1: (i) the geometry; (ii) the total energy; and (iii) the vibrational frequencies. Geometries of the isolated subsystems were taken in our previous paper from experiment; additionally it was necessary, however, to optimize the C–H and O–H bond lengths in the isolated systems. Thus, the geometry was not estimated consistently. In the present paper we have decided to perform a full optimization of the geometries of the subsystems ($CHCl_3$, CHF_3, formamide). In the complexes six intermolecular degrees of freedom, which describe entirely the mutual orientations of the subsystems, have been optimized; intramolecular coordinates were frozen at the optimum values of the isolated subsystems, with the exception of the C–H bond in CHX_3 and the N–O and N–H bonds in formamide. Geometries, total energies, and force constants for all systems were determined by means of the nonempirical SCF method, using an STO 4-31G basis set.[5] As discussed in paper 1 this basis set is sufficient for

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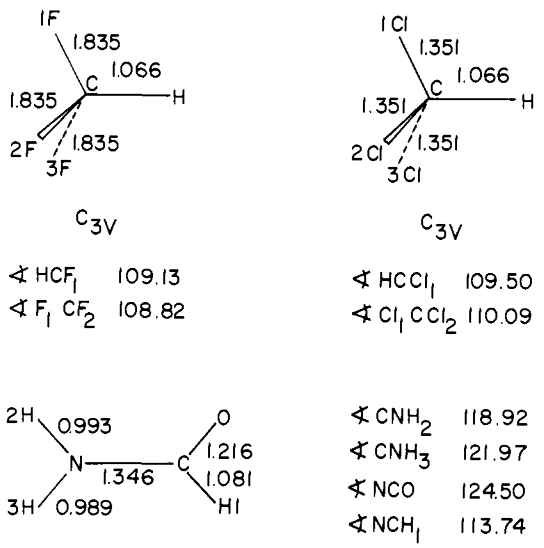

Figure 1. Geometrical parameters for CHF_3, $CHCl_3$, and formamide; distances in angstroms, angles in degrees.

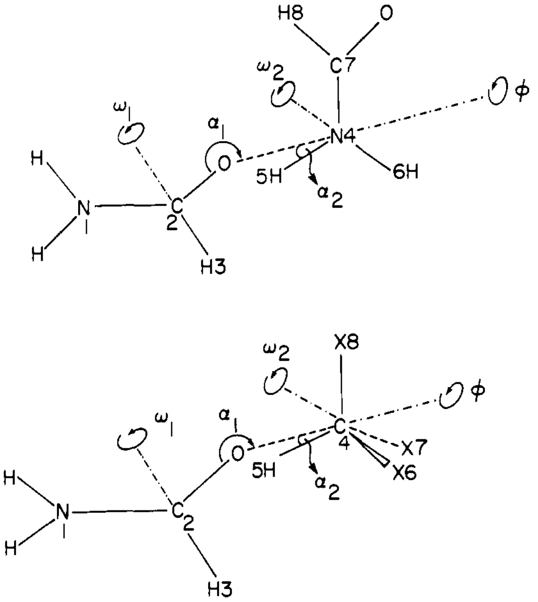

Figure 2. Intermolecular coordinates for the $H_2NCHO \cdots HNHCOH$ and $H_2NCHO \cdots HCX_3$ (X = F, Cl) complexes.

our purpose, which is the estimation of differences of two interaction energies, hence we did not use an extended basis set, which would be costly for the complexes under study. Dispersion energy contributions were evaluated by the same method as in ref 4, i.e., using ab initio multipole expansion results. The thermodynamic characteristics of the equilibrium processes were evaluated by a standard procedure described earlier.[7]

Geometry Optimizations

The geometries for CHF_3, $CHCl_3$, and formamide, optimized on the 4-31G level, are given in Figure 1. The coordinates of the complexes investigated are shown in Figure 2. Besides the six intermolecular degrees of freedom the C–O and N–H intramolecular distances were also optimized for the formamide dimer as well as the C–O and C–H distances for formamide$\cdots CHX_3$ (X = F, Cl). The geometries of the complexes studied are presented in Table I. Our results for the formamide dimer agree well with other published data[8] which originate from partial optimizations of the intermolecular coordinates with smaller than 4-31G basis sets. From the entries of Table I and Figure 1 it can be concluded that the formamide dimer and the formamide$\cdots$chloroform complex can be characterized as H-bonded complexes; the C–O bond length of the proton acceptor as well as the X–H bond length of the proton donor increases. The opposite is true for formamide$\cdots$fluoroform, where the C–H bond length of the proton donor decreases slightly.

Table I. 4-31G Theoretical Structures of $H_2NCHO \cdots HNHCOH$, $H_2NCHO \cdots HCF_3$, and $H_2NCHO \cdots HCCl_3$ complexes

	geometrical parameter[a]							
complex	R	α_1	α_2	ω_1	ω_2	ϕ	C–O	X–H
$H_2NCHO \cdots HNHCOH$	2.964	200.9	4.6	0	0	0	1.220	0.997
$H_2NCHO \cdots HCF_3$	3.109	189.5	−0.7	0	0	0	1.219	1.065
$H_2NCHO \cdots HCCl_3$	3.042	200.8	1.2	0	0	0	1.220	1.068

[a] Cf. Figure 2, distances in angstroms (=100 pm), bond angles in degree units.

Table II. SCF Stabilization Energy (ΔE^{SCF}) and Basis Set Superposition Error (BSSE)[a]

complex	$-E^{SCF}$	BSSE
$H_2NCHO \cdots HNHCOH$	8.34	*b*
$H_2NCHO \cdots HCF_3$	7.64	0.82
$H_2NCHO \cdots HCCl_3$	7.93	1.12

[a] Energies in kcal/mol (=4.184 kJ/mol). [b] Because of divergence in the SCF calculation it was impossible to determine the BSSE.

It is interesting to remark in this respect that the C–H stretching frequency in 1-H-perfluoroparaffins increases in the presence of proton acceptors instead of decreasing as is usually the case when a H bond is formed.[9]

In order to decide on the nature of the stationary points studied a vibrational FG analysis was performed (vide infra). Since all eigenvalues of the force constant matrix were positive for all complexes investigated it is evident that all the resulting structures correspond to the real minima on the respective potential energy surfaces. The question remains whether the minima found are the only ones which exist on the van der Waals (vdW) energy hypersurfaces. The formamide dimer has been chosen as a model containing a characteristic H bond of the cell membrane and we are investigating the relative effect of an addition of chloroform and fluoroform to it. In this paper we only study complexes in which the HCX_3 (X = F, Cl) molecule approaches formamide through its H atom, i.e., $H_2NCHO \cdots HCX_3$ complexes. The similar problem was studied more carefully in paper 1 for $H_2O \cdots HCX_3$ complexes; chloroform is not able to form a complex with water via Cl atoms because of negligible charges on the Cl atoms; in the case of fluoroform a competitive complex with water formed via fluorine atoms was found, but the intermolecular distance was considerably longer than in the more favorable $F_3CH \cdots OH_2$ structure.[4] Because the hydrogen atoms in formamide are less acidic than those in water we believe that the same results are valid also for the $H_2NCHO \cdots HCX_3$ (X = F, Cl) complexes.

SCF Interaction Energy

The GAUSSIAN 76 program was used.

Energy characteristics of formamide$\cdots$formamide, formamide$\cdots$chloroform, and formamide$\cdots$fluoroform are collected in Table II. Let us first discuss the reliability of ΔE^{SCF}; it is well known that ΔE^{SCF} evaluated with a 4-31G basis is overestimated but for the purpose of a calculation of an energy balance for equilibrium 1 the relative values of ΔE^{SCF} are more important

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Table III. Ab Initio and Experimental Polarizabilities[a]

		multipole polarizabilities[b]		
molecule		dipole[c] α_1 (10^{-25} cm^3)	quadrupole α_2 (10^{-42} cm^5)	octopole α_3 (10^{-59} cm^7)
CHF_3	4-31G	23.7	61.1 (1)	18.5 (3)
		(11.9)	(24.5 (1))	(5.4 (3))
	expt[d]	27.7		
$CHCl_3$	4.31G	71.5	37.9 (2)	21.9 (4)
		(34.2)	(12.7 (2)	(5.7 (4))
	expt[d]	83.3		
NH_2COH	4-31G	31.7	85.3 (1)	33.4 (3))
		(21.3)	(45.4 (1)	(13.5 (3))
	expt[d]	42.1		

[a] All results with respect to the centers of mass for 4-31G optimized geometries. [b] Calculated in the nonempirical Unsold approach.[10,11] The data in parentheses are obtained from a direct sum-over-states approach[4,10]. The numbers in parentheses denote powers of 10. [c] Calculated components (x, y, z) for the dipole polarizability (4-31G): CHF_3: 22.2, 24.4, 24.4, $CHCl_3$: 64.2, 75.1, 75.1, NH_2COH: 36.1, 21.1, 37.9. (for formamide the x and z axes are in the molecular plane; the z axis is along the N–C bond. [d] Dipole polarizabilities from: A. A. Maryott and F. Buckley, "Tables of Dielectric Constants and Electric Dipole Moments of Substances in the Gaseous State", National Bureau of Standards Circular 537, US Department of Commerce, Washington, 1953.

Table IV. Ab Initio Isotropic Dispersion Interaciton Coefficients C_n (in kcal/mol Å^n) for the Complexes Investigated Calculated in the 4-31G Basis[a]

complex	C_6	C_8	C_{10}
$H_2NCHO \cdots HNHCOH$	495.6 (1)	726.9 (2)	1034 (3)
$H_2NCHO \cdots HCF_3$	409.3 (1)	592.5 (2)	796.7 (3)
$H_2NCHO \cdots HCCl_3$	1064 (1)	2226 (2)	4140 (3)

[a] The numbers in parentheses denote powers of 10. All results are given with respect to the centers of mass.

Table V. Ab Initio Dispersion Energy Determined in the 4-31G Minimum of the SCF Potential Energy[a]

complex		dispersion energy, kcal/mol	
		undamped[b]	damped[c]
$H_2NCHO \cdots HNHCOH$	C_6R^{-6}	0.616	0.601
(R = 4.476 Å)	C_8R^{-8}	0.451	0.409
	$C_{10}R^{-10}$	0.320	0.253
	sum	1.387	1.263 (1.202)
$H_2NCHO \cdots HCF_3$	C_6R^{-6}	0.429	0.418
(R = 4.606 Å)	C_8R^{-8}	0.292	0.265
	$C_{10}R^{-10}$	0.185	0.146
	sum	0.906	0.829 (0.789)
$H_2NCHO \cdots CHCl_3$	C_6R^{-6}	0.977	0.952
(R = 4.708 Å)	C_8R^{-8}	0.922	0.836
	$C_{10}R^{-10}$	0.774	0.610
	sum	2.673	2.398 (2.283)

[a] The values R given in parentheses refer to distances between centers of mass. [b] Calculated from the isotropic interaction coefficients of Table IV. [c] Charge penetration correction for each individual term. The values in parentheses were obtained by applying an additional exchange correction (for details see ref 4)

Table VI. Total Interaction Energy (ΔE), SCF Interaction Energy (ΔE^{SCF}), and Dispersion Energy (ΔE^D) Determined in the 4-31G Minimum of the SCF Potential Energy (Energies in kcal/mol)

complex	$-\Delta E$	$-\Delta E^{SCF}$	$-\Delta E^D$
$H_2NCHO \cdots HNHCOH$	9.54	8.34	1.20
$H_2NCHO \cdots HCF_3$	8.43	7.64	0.79
$H_2NCHO \cdots HCCl_3$	10.21	7.93	2.28

than the respective absolute values. In our previous study[4] it was concluded that the relative values of the 4-31G ΔE^{SCF} are sound. Further, it is known that ΔE^{SCF} calculated with medium size basis sets is deteriorated by the so called basis set superposition error (BSSE).[6] The data of Table II show rather small BSSE values for all complexes investigated, which underlines the suitability of the 4-31G basis set; in the following thermodynamic treatment we have used therefore ΔE^{SCF} without taking into account the BSSE. We have optimized all intermolecular degrees of freedom plus two intermolecular ones; the question arises how great an error is introduced by freezing the remaining intramolecular degrees of freedom. It was shown[4] that for the water dimer this error represents less than 2% of the optimized ΔE^{SCF}. An error of the same magnitude can be expected for the present complexes. From Table II it is evident that at the SCF level the formamide dimer is stabilized slightly more than the other complexes; taking into account the BSSE formamide$\cdots$chloroform and formamide$\cdots$fluoroform are equally stabilized.

Dispersion Interaction Energy

The multipole dispersion energies were calculated isotropically; the expression used for calculating the long-range dispersion energy in the nonempirical Unsöld method was given in the previous paper.[4] The calculated (Unsöld approach[10,12] 4-31G basis set) and experimental multipole polarizabilities are collected in Table III. Table IV contains the calculated isotropic dispersion interaction coefficients (4-31G) for the complexes. Table V constains the numerical values of the C_6R^{-6}, C_8R^{-8}, and $C_{10}R^{-10}$ energy terms evaluated at the SCF potential energy minimum. It is known that the multipole expansion frequently shows a slow convergence or even divergence; the expansion in general is asymptotically divergent.[13,14] In our previous paper we have met serious problems with the convergence for $(H_2O)_2$ and $CF_3H\cdots OH_2$; the expansion diverged strongly for $CCl_3\cdots OH_2$. From the data of Table V it is seen that the expansion converges for all complexes presently under study. This seemingly surprising result could be explained by the fact that the distances between the centers of mass for these complexes are considerably larger than those of the complexes studied in ref 4. The serious problems with convergence for $H_2O\cdots H_2O$ and $H_2O\cdots HCX_3$ (X = F, Cl) forced us to use damping techniques which in ref 4 clearly required different damping functions for the C_6R^{-6}, C_8R^{-8}, and $C_{10}R^{-10}$ terms. For this damping method two scaling factors were proposed originally.[15] The use of $\rho = \rho_8/\rho_6$ results in too strong a damping for the present complex. We have therefore used the other scaling factor, namely $\rho = \rho_m = R_m^{H\cdots H}/R_m^{A\cdots B}$ (R_m is the distance at the potential minimum for $H\cdots H$ for the complex studied); the results are also given in Table V.

Let us finally comment on the use of the isotropic dispersion energy instead of the anisotropic energy. The dispersion energy will not be very anisotropic, as could be inferred from the different calculated components of the dipole polarizabilities (footnote *c* of Table III). Only for formamide is the out-of-plane component (y) significantly smaller than the in-plane components (x, z). This means that the dispersion energy for the structures found in this paper is slightly underestimated by using the isotropic dispersion energy. This was happened, however, in a uniform way for all complexes studied. For a brief discussion of this point see ref 4.

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Table VII. Wavenumbers of Intermolecular and Some Intramolecular Vibrations (cm^{-1})

complex	wavenumbers							
	intermolecular						intramolecular	
							C-O[a]	X-H[b]
$H_2NCHO\cdots HNHCOH$	97	130	161	234	356	505	1829	3795
$H_2NCHO\cdots HCF_3$	45	63	125	126	232	1585	1831	3455
$H_2NCHO\cdots HCCl_3$	26	34	111	121	196	1184	1834	3420

[a] The calculated C=O stretching frequency for isolated H_2NCHO is equal to 1834 cm^{-1}. [b] N-H and C-H stretching in isolated H_2NCHO, CHF_3, and $CHCl_3$ equal to 3917, 3420, and 3455 cm^{-1} respectively.

Table VIII. Thermodynamic Characteristics of the $H_2NCHO\cdots HNHCOH + A \rightleftharpoons H_2NCHO\cdots A + H_2NCOH$ Process[a]

process	T, K	ΔE, kcal/mol	$\Delta H°$, kcal/mol	$T\Delta S°$, kcal/mol	$\Delta G°$, kcal/mol	log K
$H_2NCHO\cdots HNHCOH + CF_3H \rightleftharpoons H_2NCHO\cdots HCF_3 + H_2NCOH$	100	1.11	2.52	0.49	2.03	−4.42
	298		2.59	1.67	0.92	−0.67
$H_2NCHO\cdots HNHCOH + CCl_3H \rightleftharpoons H_2NCHO\cdots HCCl_3 + H_2NCOH$	100	−0.67	0.00	0.53	−0.53	1.15
	298		0.12	1.86	−1.74	1.28

[a] ΔE was calculated on the SCF (4-31G) + dispersion energy level. Remaining molecular characteristics were evaluated on the SCF 4-31G level.

Total Interaction Energy

The total interaction energies constructed as sums of SCF interaction energies and dispersion energies determined for the 4-31G SCF potential energy minimum are given in Table VI. From a theoretical point of view it is more reliable to optimize ΔE instead of ΔE^{SCF}. We have performed, therefore, a pilot calculation for the formamide dimer. The inclusion of the dispersion energy changed the intermolecular distance negligibly, and consequently one cannot expect an important change of $\Delta E = \Delta E^{SCF} + E^{D}$. Considering the ΔE values the crucial role of the dispersion energy is apparent. Whereas the SCF energy stabilizes formamide···fluoroform and formamide···chloroform almost equally, the ΔE for these complexes are different. This difference is essential for our purposes.

Finally, we should like to reiterate our previously made comment[4] that, although the absolute values of the ΔE are not very accurate, due primarily to ΔE^{SCF}, the relative values of the ΔE are meaningful. The results of Table VI are used in the thermodynamic calculations.

The Wilson FG Analysis

The coordinates assumed in the vibrational FG analysis are as follows: formamide dimer, internal coordinates R_{24}, ϕ_{324}, ϕ_{642}, τ_{1324}, τ_{3246}, τ_{2467}; formamide···CHX_3 (X = F, Cl), symmetry coordinates $S_1(A) = R_{24}$, $S_2(A') = \phi_{324}$, $S_3(A') = 1/\sqrt{2}(\phi_{642} + \phi_{742})$; $S_1(A') = 1/\sqrt{2}(\phi_{642} - \phi_{742})$, $S_2(A'') = \tau_{1324}$, $S_3(A'') = \tau_{3248}$. Besides the six intermolecular coordinates mentioned, two intramolecular coordinates were optimized—namely those which are influenced most strongly by complex formation. In Table VII are collected the 4-31G intermolecular vibrational frequencies for all complexes mentioned as well as the intramolecular stretching frequencies of the proton donor and proton acceptor. When comparing the proton donor stretching frequencies in the isolated and bound subsystems it is seen that the formamide dimer as well as the formamide···chloroform complex exhibit a characteristic feature of a H bond: the decrease of the wavenumber of the X–H bond of the proton donor upon complex formation. The opposite is true, however, for formamide···fluoroform. On the basis of this fact and the above mentioned decrease of the C–H bond length upon complex formation it can be concluded that fluoroform does not form a hydrogen bond with formamide. The same has been found for the $CHF_3\cdots OH_2$ complex.

Thermodynamic Treatment

The calculated characteristics of process 1 are collected in Table VIII. They were obtained by means of partition functions computed from the SCF (4-31G) and SCF (4-31G) + dispersion energy molecular constants. Rigid rotator, harmonic oscillator, and ideal gas approximations were adopted.

From the entries of Table VIII it is clear that $CHCl_3$ is able to break the H bond in the formamide dimer at both temperatures considered. For CHF_3 it appears that this system is almost unable to perturb the H bond at 100 K; although this ability increases with increasing temperature it is still small at 298 K. Comparing the action of CHF_3 and $CHCl_3$ it is evident that the differences originate mainly from different $\Delta H°$ values. It is appropriate to restate that it is the dispersion energy that is responsible for the differences between ΔE for the $H_2NCHO\cdots HCF_3$ and $H_2NCHO\cdots HCCl_3$ complexes.

Conclusion

The results presented in this paper substantiate the contention that general anesthetics containing an acidic hydrogen are able to perturb ("break") N—H···O=C H bonds. The most potent general anesthetics, chloroform, halothane, methoxyflurane, and others, belong to this category. Since N—H···O=C type H bonds play a most important role in determining the structure of proteins and since the ion channels in the nerve cell membrane are formed by proteins this is bound to be important for the mechanism of anesthesia.

Registry No. $CHCl_3$, 67-66-3; CHF_3, 75-46-7; NH_2COH, 75-12-7.