repulsive. Scaling these to make them less repulsive seems to overstabilize the d orbitals, allowing too much d occupation in sulfoxides and sulfones. In molecules in which the sulfur is in a highly electron-withdrawing environment such as SOF_2 and SO_3 and ions such as $S_2O_3^{2-}$, SO_4^{2-}, U_d is positive (attractive). Both U_d and ζ_d show that in thiourea the d orbitals are extremely diffuse. The slight involvement of d orbitals in the sulfur atoms of thioketones is reflected in the small values ζ_d of thioformaldelyde and the thioketo sulfur atom of the pyranthiones. Little difference is seen between alkyl- and arylthiols in the contraction or occupation of the d orbitals. The S atoms in aryl thioether, with a 3d orbital exponent of 0.85, are similar to thiol sulfur. 3d occupations of 0.26–0.27 indicate a minimal degree of coupling between ring and methyl p orbitals through sulfur.

In thiophene, the $C_2 - C_3$ $p\pi$–$p\pi$ bond has a population of 0.27, compared with a population of 0.18 for the $d_{xz}\pi$–$p\pi$ and 0.03 for the $d_{xy}\pi$–$p\ \pi$ "bonds". This is not surprising in view of the C–S bond length used in this calculation, which was the experimental value of 1.720 Å. As in S atoms in aryl thioethers, sulfur d orbitals have an occupation of 0.26 in thiophene, which indicates a minimal degree of coupling of the π-bond system through sulfur.

There is little difference between the calculated spectra of thiophenol and phenol (Table II). The transitions with appreciable oscillator strength are $\pi \rightarrow \pi^*$ involving ring orbitals almost exclusively. This means, as in phenol, the first transition (^1L_b) and the high-intensity transitions (^1B) in thiophenol are fairly well placed, but the (^1L_a) transition has failed to come down in energy. This pattern holds for the sulfoxide. The second ring $\pi \rightarrow \pi^*$ transition in thiophenol, observed at 4.9 eV, is calculated at 5.9 eV. In addition, there is a calculated charge-transfer band which is not seen in the experimental (liquid-phase) UV spectrum. The agreement between calculated and experimental spectra in the sulfone is good, although the intense band occurs at 5.9 eV in both thiophenol and methyl phenyl sulfone; the orbital nature of the states involved differs considerably in the two compounds.

In the pyran series of molecules in Table II, certain trends are apparent: first, in pyran-4*H*-one, the $^1A_1$ transition is calculated at an energy which is significantly too high. This also occurs in thiopyran-4*H*-one and seems to be a function of the keto group. The same effect is seen in both of the thiopyranthiones, although the disagreement is less pronounced. The $^1A_1$ transition in all these molecules involves transfer of electron density from the ring heteroatom to the ring double bonds.

Thus, the method developed appears to provide qualitative and semiquantitative insights into the special problems arising in the second period, especially those generated by the d orbitals.

Quantum Chemical and Statistical Thermodynamic Investigations of Anesthetic Activity. 1. The Interaction between Chloroform, Fluoroform, Cyclopropane, and an O-H···O Hydrogen Bond

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Abstract: It has been postulated that molecules having anesthetic potency are able to perturb or dissociate hydrogen bonds and that this is a factor in the mechanism of anesthesia. The equilibrium for a water dimer interacting with two potent anesthetics, chloroform or cyclopropane, and fluoroform, a molecule having no anesthetic potency, is examined by quantum chemical and statistical thermodynamic means. It is shown that the $\Delta G°$ values related to the "breaking" process and the extent of mixed dimer formation parallel the known anesthetic potencies of the three compounds.

I. Introduction

General anesthesia is a reversible perturbation of the nervous system. When an understanding of its mechanism is sought at the molecular level, two striking facts should be accounted for: (a) anesthetic action occurs without actual chemical reaction; (b) general anesthetics do not belong to any one common chemical type. Both facts indicate that the mechanism of anesthesia is connected with changes in molecular associations rather than the formation or breaking of covalent chemical bonds. While there seems to be general consensus on this point, the nature of the associations which are involved is still a subject for current investigations. (For recent reviews, see ref 4–8.)

For several years the theory adhered to by most researchers in the field was the unitary hypothesis based on interactions with the hydrophobic part of the cell membrane only. This originated with the well-known relationship between anesthetic potency and lipid solubility. In recent years, however, it became apparent that polar interactions are also important for the mechanism of anesthesia, especially if more potent anesthetics are involved.[9-21]

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(4) K. W. Miller and E. B. Smith in "A Guide to Molecular Pharmacology-Toxicology", Part 2, R. M. Featherstone, Ed., Marcel Dekker, New York, 1973, pp 427–475.

(5) M. J. Halsey in "Anesthetic Uptake and Action", E. I. Eger, Ed., Williams and Wilkins, Baltimore, 1974, pp 45–76.

(6) J. C. Miller and K. W. Miller in "Physiological and Pharmacological Biochemistry", H. K. F. Blaschko, Ed., Butterworths, London, 1975, pp 33–75.

(7) R. D. Kaufman, *Anesthesiology*, **46**, 49 (1977).

(8) D. D. Denson, *Chemtech.*, **8**, 446 (1977).

(9) T. Di Paolo and C. Sandorfy, *J. Med. Chem.*, **17**, 809 (1974).

(10) T. Di Paolo and C. Sandorfy, *Can. J. Chem.*, **52**, 3612 (1974).

(11) C. Hansch, A. Vittoria, C. Silipo, and P. Y. C. Jow, *J. Med. Chem.*, **18**, 546 (1975).

(12) R. H. Davies, R. D. Bagnall, and W. G. M. Jones, *Int. J. Quantum Chem, Quantum Biol. Symp.*, No. **1**, 201 (1974).

(13) R. H. Davies, R. D. Bagnall, W. Bell, and W. G. M. Jones, *Int. J. Quantum. Chem., Quantum Biol. Symp.*, No. **3**, 171 (1976).

(14) R. Massuda and C. Sandorfy, *Can. J. Chem.*, **55**, 3211 (1977).

(15) A. Nagyrevi and C. Sandorfy, *Can. J. Chem.*, **55**, 1592 (1977).

0002-7863/81/1503-1360$01.25/0

Consequently a more general theory is needed based on all types of van der Waals associations, hydrogen bonding and, perhaps, charge-transfer type interactions. In particular the role of the so-called acidic hydrogen which is present in several of the most efficient anesthetics like chloroform, halothane, and methoxyfluran has been examined.

It was observed in this laboratory that general anesthetics of the halofluorocarbon type perturb or dissociate hydrogen bonds of the N—H···O=C, N—H···N, and O—H···O types.[9,10,18,19] These can also involve water and can be regarded as models for the hydrogen bonds that (among other interactions) are necessary to ensure the right conformations of the macromolecules forming the nerve cell membrane. These, in turn, control the dimensions of the ion channels and the permeability of the membrane on which the functioning of the nervous system depends. This phenomenon has been the object of a series of spectroscopic studies, and a relationship with anesthetic potency could be established. Therefore it has been decided to subject the interaction of an anesthetic with a hydrogen bond to close scrutiny by the methods of quantum chemistry and statistical thermodynamics.

In this paper the hydrogen bond in the water dimer has been chosen as the target. It can be considered as a model for hydrogen bonds in the outer spheres of the water clusters surrounding the polar heads of lipids or of O—H···O-type H bonds involving the OH groups in the side chains of some aminoacid residues. In our second paper a peptide-type H bond (N—H···O=C) will be considered. These systems will be put into contact with three perturbers: chloroform (a potent anesthetic containing the acidic hydrogen), fluoroform (no anesthetic potency), and cyclopropane (a good anesthetic with no acidic hydrogen). It is in order to point out in this respect that our calculations apply to one isolated water dimer and the behavior of the H-bond it contains with respect to perturbers. Transition from our model to condensed phases is not straightforward. For this reason correlations with thermodynamic or other physicochemical bulk properties of water of chloroform will not be sought. This paper is a search for an answer to the following question: can it be expected on theoretical ground that certain H bonds are broken or perturbed by typical anesthetics and replaced by other H bonds or molecular associations of a different type? Whatever way the anesthetic reaches the nerve cell membrane such interactions must eventually occur.

II. Outline of the Work

The ability of a compound A to break the hydrogen bond in the $(H_2O)_2$ dimer by forming a competitive complex $H_2O{\cdots}A$, at temperature T (equilibrium 1) is determined by the equilibrium

$$H_2O{\cdots}H_2O + A \overset{K_T}{\rightleftharpoons} H_2O{\cdots}A + H_2O \qquad (1)$$

constant K_T or according to relation 2 by the corresponding change

$$\Delta G_T{}^{\circ} = -RT \ln K_T \qquad (2)$$

of the Gibbs free energy, ΔG°. In order to determine ΔG° for equilibrium 1, it is necessary to know (i) the geometries, (ii) the total energies, and (iii) the frequencies of normal vibrational modes, for all systems involved. Geometries, as well as total energies, are evaluated quantum chemically (see sections III–VI), vibrational frequencies are determined by an FG analysis (section VII), and the thermodynamic treatment is described in Sections VIII and IX.

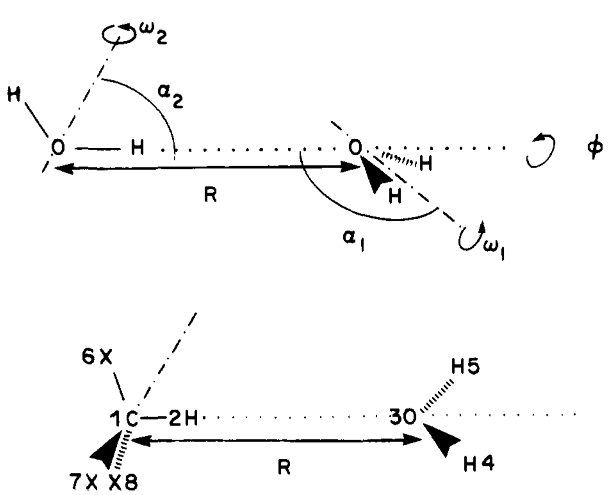

Figure 1. Internal coordinates for the $H_2O{\cdots}H_2O$ and $CHX_3{\cdots}H_2O$ (X = F, Cl) complexes. For $CHX_3{\cdots}H_2O$ we have assumed the following symmetry coordinates: $S_1(A') = R$; $S_2(A') = 1/2^{1/2}(\varphi_{713} + \varphi_{813})$; $S_3(A') = \tau_{4315}$; $S_1(A'') = 1/2^{1/2}(\varphi_{713} - \varphi_{813})$; $S_2(A'') = 1/2^{1/2}(\varphi_{134} - \varphi_{135})$; $S_3(A'') = 1/6^{1/2}(\tau_{6134} + \tau_{7134} + \tau_{8134} + \tau_{6135} + \tau_{7135} + \tau_{8135})$.

Table I. Theoretical Structures of $HOH{\cdots}OH_2$, $CF_3H{\cdots}OH_2$, and $CCl_3H{\cdots}OH_2$ Complexes

geometrical parameter[a]	R_m	α_1	α_2	ω_1	ω_2	ϕ	X-H[b]
$HOH{\cdots}H_2O$	2.840	144	52	90	0	180	0.961
geometrical parameter[a,b]	R_m	φ_{713}	φ_{813}	φ_{134}	φ_{135}	τ_{4315}	X-H[b]
$CF_3H{\cdots}OH_2$	3.168	109	109	128	128	180	1.068
$CCl_3H{\cdots}OH_2$	3.070	109	109	128	128	180	1.069

[a] Cf. Figure 1, bond lengths in Å (=100 pm), bond angles in degree units. [b] X–H bond length in the proton donor; the respective optimized 4-31G bond lengths in H_2O, CF_3H, and CCl_3H are 0.955, 1.068, and 1.066 Å. [c] The water molecule rotates completely freely in both complexes.

Before starting the description of the calculations let us make one comment concerning the basic philosophy of this paper. The intramolecular geometry of each subsystem was kept constant (with the exception of the X–H bond, cf. Section III), and only intermolecular coordinates were optimized. Owing to the presence of the same subsystems on both sides of equilibrium 1, the subsystem characteristics cancel. For example, the energetic balance of the equilibrium is determined almost completely by the difference of the stabilization energies of the complexes $H_2O{\cdots}A$ and $H_2O{\cdots}H_2O$. Therefore for our purposes reliable relative values of stabilization energies of $H_2O{\cdots}A$ and $H_2O{\cdots}H_2O$ are more important than good absolute values. The same is valid for vibrational frequencies.

The nonempirical SCF method using the STO 4-31G basis set[22] was used in the calculations of the equilibrium geometries, total energies, and the force constants of all complexes under study (for some points on the potential energy hypersurfaces for the complexes total energies were also calculated with a 4-31G* basis set[23]). The superposition errors, $\Delta\epsilon$, were estimated by the function counterpoise method[24] at the minima on the van der Waals (vdW) potential energy hypersurfaces. Dispersion energies were calculated nonempirically in the multipole expansion and were added to the SCF interaction energies. The thermodynamic characteristics of the equilibrium processes were obtained by a standard procedure described elsewhere.[25] The partition function for free internal rotation and the respective contribution to the

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(16) J. M. Brown and P. A. Chaloner, *Can. J. Chem.*, **55**, 3380 (1977).

(17) L. S. Koehler, W. Curley, and K. A. Koehler, *Mol. Pharmacol.*, **13**, 113 (1977).

(18) C. Sandorfy, *Anesthesiology*, **48**, 357 (1978).

(19) G. Trudeau, K. C. Cole, R. Massuda, and C. Sandorfy, *Can. J. Chem.*, **56**, 1681 (1978).

(20) G. Trudeau, P. Dupuis, C. Sandorfy, J. M. Dumas, and M. Guērin, *Top. Curr. Chem.*, **93** (1980).

(21) R. Bicca de Alencastro and C. Sandorfy, *Can. J. Chem.*, **50**, 3594 (1972).

(22) R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.* **54**, 724 (1971).

(23) P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta*, **28**, 213 (1973).

(24) S. F. Boys and F. Bernardi, *Mol. Phys.*, **19**, 553 (1970); A. Johansson, P. Kollman, and S. Rothenberg, *Theor. Chim. Acta*, **29**, 167 (1973); M. Urban and P. Hobza, *ibid.*, **36**, 215 (1975).

(25) P. Carsky, R. Zahradnik, M. Urban, and V. Kellö, *Collect. Czech. Chem. Commun.*, 43, 1965 (1978).

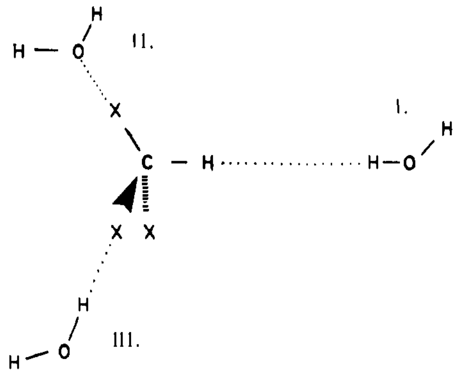

Figure 2. Alternative approaches of the H_2O molecule to the CX_3H (X = F, Cl).

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

	basis set					
	4-31G		4-31G*[b]		4-31G*[c]	
	$-\Delta E^{SCF}$	$\Delta\epsilon$	$-\Delta E^{SCF}$	$\Delta\epsilon$	$-\Delta E^{SCF}$	$\Delta\epsilon$
$HOH\cdots OH_2$	8.08	0.90	5.75	1.10	5.95	1.57
$CF_3H\cdots OH_2$	6.58[d]	0.74	3.53	0.75	3.85	
$CCl_3H\cdots OH_2$	7.00	0.98	4.03		4.38	

[a] Energies in kcal/mol (=4.184 kJ/mol). [b] 4-31G optimized geometry used. [c] 4-31G optimized geometry used with a reoptimized intermolecular distance; the following values of R (cf. Figure 1) were found for $HOH\cdots OH_2$, $CF_3H\cdots OH_2$, and $CCl_3H\cdots OH_2$; 2.955, 3.332, and 3.240 Å. [d] The stabilization energy of $CF_3H\cdots HOH$ (Figure 2, approach III) equals to −2.32 kcal/mol.

thermodynamic characteristics were determined according to Pitzer.[26]

III. Geometry Optimizations

The geometrical parameters for $H_2O\cdots H_2O$, $CF_3H\cdots OH_2$, and $CCl_3H\cdots OH_2$ complexes (Figure 1) determined on the 4-31G level are summarized in Table I. Six intermolecular parameters, which describe completely the mutual orientation of the two subsystems, were optimized. The geometries of the subsystems were kept fixed at the experimental ones (H_2O,[27] CF_3H,[27] CCl_3H,[29] cyclopropane[30]) except for the X–H bond lengths (X = O, Cl, F) in the X–H···O hydrogen bonds, which were optimized both in the monomers and the complexes. Only for $HOH\cdots OH_2$ and $CCl_3H\cdots OH_2$ have we found an increase of the X–H bond length (in comparison with the optimized X–H bond length in the isolated subsystem) typical for a H bond formation.

The question arises whether the structures found correspond to real minima on the potential energy hypersurfaces. It was found that all eigenvalues of the force constant matrix for all complexes investigated are positive. This unambiguously means that the structures found are real minima.[31] Another question which has to be asked is whether the minima found are the only ones which exist on the respective potential energy hypersurfaces. For $(H_2O)_2$ there is enough evidence[32,33] that only one minimum exists on its energy hypersurface corresponding to a "linear" structure. This structure was investigated carefully (including an optimization of the intramolecular parameters) by Curtiss and Pople[34] using the 4-31G basis set; the agreement between the present values (Table I) and those of ref 34 is good. For CF_3H and CCl_3H three different approaches to the water molecule were investigated (see Figure 2) where only the C···O distances were optimized. For CCl_3H neither approach I nor II or III leads to a complex formation. This is not surprising if we keep in mind the atomic charges on CCl_3H (4-31G: H, 0.44 +, Cl, 0.04 +, C, 0.54 − e). For CF_3H approach III results in a stabilization but the C···O distance (4.41 Å) is considerably longer than for the structure in Figure 1.

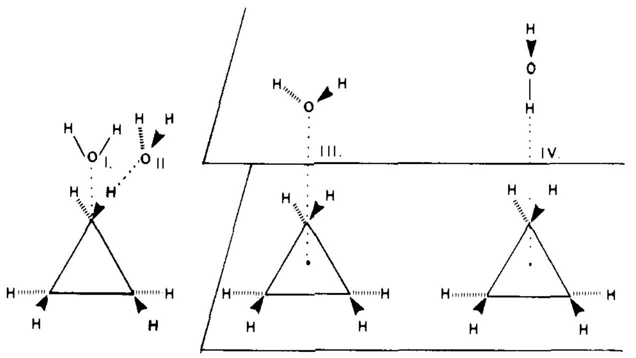

Figure 3. Structures investigated for the cyclopropane···water complex.

Table III. Theoretical Characteristics of the $c\text{-}C_3H_6\cdots OH_2$ Complex

structure[a]	R_m[b]	$-\Delta E^{SCF}$ (4-31G)[c]	$-\Delta E^{SCF}$ (4-31G*)[c]
I	3.550	0.41	
II	3.689	1.29	
III	3.496[d]	1.42[d]	1.15[d]
IV	no stabilization		

[a] See Figure 3. [b] The distances (in Å) for structures I and II are C···O distances, for structures III and IV distances between the center of mass of cyclopropane and oxygen in water. [c] Energy in kcal/mol. [d] Optimization using 4-31G* results in slightly changed characteristics. $R_m = 3.510$ Å; $\Delta E = 1.15$ kcal/mol.

IV. SCF Interaction Energy

The energetical characteristics of $(H_2O)_2$, $CF_3H\cdots OH_2$, and $CCl_3\cdots OH_2$ are collected in Table II. Only for $(H_2O)_2$ can our results be compared with previous calculations. A complete optimization[34] of all coordinates (intramolecular and intermolecular) in the 4-31G basis set resulted in a stabilization energy of −8.2 kcal/mol. Hence, the freezing of all intramolecular coordinates (except for the O–H bond length) affects the stabilization energy by less than 2% in this particular case. One could expect this to be even less pronounced for the weaker complexes $CF_3H\cdots OH_2$ and $CCl_3H\cdots OH_2$. For all complexes the absolute value of ΔE is overestimated (see section VI). For instance, for $(H_2O)_2$ the Hartree–Fock (HF) limit of ΔE is estimated[35] to be −3.9 kcal/mol. Moreover, for $(H_2O)_2$ the calculated ΔE in the 6-31G* basis set[34] (−5.6 kcal/mol) is not very different from the 4-31G* result (see Table II), both being closer to the HF limit value than the 4-31G result. Extending the basis from 4-31G to 4-31G* yields a rather equal absolute decrease in ΔE for all complexes, even for $CCl_3H\cdots OH_2$ for which one would expect a more pronounced role of the d functions. Therefore, even though the absolute values of ΔE in the 4-31G basis are overestimated, this apparently happens in a consistent way for all complexes under study, and so the relative values of ΔE (or differences of ΔE), which are of interest for this paper, are not significantly affected.

Let us further investigate the values of the basis set superposition error, $\Delta\epsilon$. In the 4-31G basis $\Delta\epsilon$ is rather small and is almost the same for the different complexes. It again confirms the ability

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[26] K. S. Pitzer, "Quantum Chemistry", Prentice Hall, New York, 1954, p 492.

[27] W. S. Benedict, N. Gailar, and E. K. Plyler, *J. Chem. Phys.*, **24**, 1139 (1956).

[28] S. N. Ghosh, R. Trambarulo, and W. Gordy, *J. Chem. Phys.*, **20**, 605 (1952).

[29] K. H. Schmidt and A. Müller, *J. Mol. Spectrosc.*, **50**, 115 (1974).

[30] O. Bastiansen, F. N. Fritsch, and K. Hedberg, *Acta Crystallogr.*, **17**, 538 (1964).

[31] P. Hobza and R. Zahradnik, *Top. Curr. Chem.*, **93** (1980).

[32] L. L Shipman, J. C. Owicki, and H. A. Scheraga, *J. Phys. Chem.*, **78**, 2055 (1974).

[33] R. C. Kerns and L. C. Allen, *J. Am. Chem. Soc.*, **100**, 6587 (1978).

[34] L. A. Curtiss and J. A. Pople, *J. Mol. Spectrosc.*, **55**, 1 (1975).

[35] H. Popkie, H. Kistenmacher, and E. Clementi, *J. Chem. Phys.*, **59**, 1325 (1973).

Table IV. Ab initio and Experimental Molecular Multipole Properties[a]

		multipole polarizabilities[b]			
molecule		dipole[c] α_1, 10^{-25} cm^3	quadrupole α_2, 10^{-42} cm^5	octupole α_3, 10^{-59} cm^7	dipole moment μ, D
H_2O	4-31G	9.08 (4.40)	8.15 (1) (2.55 (1))	20.2 (2) (2.2 (2))	2.61
	expt[e]	14.5			1.85
	4-31G*	7.22	6.98 (1)	16.1 (2)	2.19
CHF_3	4-31G	23.7 (11.9)	61.1 (1) (24.5 (1))	18.5 (3) (5.4 (3))	2.11
	expt[e]	27.7			1.65
$CHCl_3$	4-31G	71.5 (34.2)	37.9 (2) (12.7 (2))	(21.9 (4)) (5.7 (4))	1.72
	expt[e]	83.3			1.04
C_3H_6	4-31G	44.6 (34.9)	14.2 (2) (8.8 (2))	67.4 (3)) (29.8 (3))	0
	expt[e]	55.1			0
	4-31G*	41.5	13.6 (2)	64.7 (3)	0

[a] All results with respect to the centers of mass for experimental geometries[27-30] (except for the X–H bonds, see Table I, footnote *b*). [b] Calculated in the nonempirical Unsold approach.[43-47] The results in parentheses (second entries) are obtained from a direct sum-over-state approach.[43,44] The numbers in parentheses denote powers of 10. [c] Calculated components (x, y, and z) for the dipole polarizability (4-31G basis): H_2O, 10.4, 11.3, 5.56 (too anisotropic as compared with the accurate values CHF_3, 22.2, anisotropic as compared with the accurate values of ref 42, 14.3, 14.5, and 14.2); CHF_3, 22.2, 24.4, 24.4; $CHCl_3$, 64.2, 75.1, 75.1; c-C_3H_6, 45.8, 45.8, 42.2 (for H_2O the X and Y axes are in the molecular plane; the X axis is the C_{2v} axis). [d] 1 D = 10^{-18} esu cm = 0.39343 au. [e] Dipole polarizabilities from: A. A. Maryott and F. Buckley, *Natl. Bur. Stand. (U.S.) Circ.* No. 537 (1953). Dipole moments from A. L. McClellan, "Tables of Experimental Dipole Moments", Vol. 2, Rahara Enterprises, California, 1974.

Table V. Ab Initio Isotropic Dispersion Interaction Coefficients C_n[a] (in kcal/(mol Å^n)), Calculated in the 4-31G Basis[b]

	H_2O	c-C_3H_6	CHF_3	$CHCl_3$
C_6	50.42 (1)[c]	210.8 (1)	131.3 (1)	334.9 (1)
H_2O C_8	24.30 (2)	230.1 (2)	125.6 (2)	538.3 (2)
C_{10}	15.22 (3)	254.1 (3)	112.2 (3)	741.3 (3)
	C_6	901.1 (1)[c]	549.1 (1)	1437 (1)
	c-C_3H_6 C_8	1524 (2)	854.9 (2)	3168 (2)
	C_{10}	2512 (3)	1246 (3)	6271 (3)
	H_2O (DZ)[d]	C_6	341.9 (1)	874.8 (1)
		CHF_3 C_8	489.1 (2)	1809 (2)
C_6	59.99 (1)[c]	C_{10}	620.1 (3)	3247 (3)
H_2O C_8	29.75 (2)			
(DZ) C_{10}	18.97 (3)			
			C_6	2291 (1)
			$CHCl_3$ C_8	6227 (2)
			C_{10}	14740 (3)
		c-C_3H_6 (DZ)[d]		
	C_6	983.0 (1)		
	c-C_3H_6 C_8	1670 (2)		
	(DZ) C_{10}	2767 (3)		

[a] $C_n = \Sigma_{l_A,l_B}^{2l_A+2l_B+2=n} C_n(l_A,l_B)$, see eq 3 and 4. The numbers in parentheses denote powers of 10. [b] All results with respect to the centers of mass. 1 kcal/(mol Å^n) = $(627.51)^{-1} \times (0.529\ 177)^{-n}$ au. [c] Accurate empirical values for C_6 are 62.52 (1) kcal/(mol Å^6) for $(H_2O)_2$ (DOSD)[51] and 869.2 (1) kcal/(mol Å^6) for (c-C_3H_6)$_2$ (from refractivity).[52] [d] Results from a double-ζ (DZ) Huzinaga-Dunning basis set.[50]

of the 4-31G basis set to predict reasonably well the relative values of ΔE. Suprisingly large values for $\Delta\epsilon$ were found in the 4-31G* basis which could probably be ascribed to the unbalanced character of the 4-31G* basis (an unbalance between the sp and d parts of 4-31G*[36] and the lack of p functions on the hydrogens). Let us add, however, that large values of $\Delta\epsilon$ were also found for $(H_2O)_2$ in the 6-31G* basis.[37] It seems, therefore, that the reason for the large $\Delta\epsilon$ with "star" basis sets should be sought in the very nature of those basis sets.

The structures investigated for c-$C_3H_6 \cdots H_2O$ are depicted in Figure 3; the optimized intermolecular distances and stabilization energies are given in Table III. From this table we can learn that the stabilization energies of this complex, calculated on the SCF level, are rather small. The most stable structure corresponds to a sandwich-type complex (III in Figure 3) and not to a H bond like complex (II in Figure 3). An interesting point is that the potential energy curve corresponding to the sandwich-type approach of water to cyclopropane is very flat. Reducing the intermolecular distance by almost 0.5 Å (from 3.496 to 3.0 Å) still results in a negative ΔE (−0.14 kcal/mol)! The sandwich complex is of prime importance due to the rather small distance between the centers of mass of the subsystems (3.6 Å) as compared with the other structures (I, 4.1 Å; II, 4.3 Å). In the next section we shall see that for structure III (cf. Figure 3) it is the dispersion energy (being proportional to R^{-n}) which is the major contribution to the total stabilization energy. A basis set extension from 4-31G to 4-31G* results in only minor changes of both ΔE and R.

V. Dispersion Interaction Energy and Molecular Multipole Properties

In the previous section the interaction energies of the different complexes were given on the SCF level. The classical long-range interactions of electrostatic and induction types are included in such a treatment but not the dispersion interactions. Yet these interactions can play an important role for hydrogen-bonded systems.[38-40] A full ab initio second-order (sum-over-states) perturbation-type calculation of the dispersion energy for these complexes (using the SCF MO's for the subsystems and the complete set of two-electron integrals calculated for the complex) would require much computing time. Moreover the results would not be very meaningful, since the 4-31G (and also 4-31G*) basis sets are far from complete;[41-44] as a consequence the sum-over-states polarizabilities, calculated according to the Møller–Plesset perturbation theory in which the excitation energies are simply given as orbital energy differences[43,45,46] are much too small (see Table IV, values in parentheses), and the dispersion energies would also be drastically underestimated. An approximate ab initio calculation of the dispersion energy is possible, however, when the multipole expansion for the intermolecular interaction operator is used, whereby assuming that the molecular charge clouds do not overlap. In this approach the problem of an incomplete AO basis set can be overcome, for instance, by employing the nonempirical Unsöld method,[43,47] which we will apply is this section.

For the purposes of this paper it will be sufficient if an estimate can be made of at least the right order of magnitude of the dispersion interactions for the different complexes. So we decided to compute the dispersion energy only isotropically (averaged over all relative orientations of the molecules), and to add these, in section VI, to the SCF interaction energies of Table III. The

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(36) P. Pulay, G. Fogarasi, F. Pang, and J. E. Boggs, *J. Am. Chem. Soc.*, **101**, 2550 (1979).

(37) P. Hobza, unpublished results, 1979.

(38) O. Matsuoka, E. Clementi, and M. Yoshimine, *J. Chem. Phys.*, **64**, 1351 (1976).

(39) B. Jeziorski and M. C. van Hemert, *Mol. Phys.*, **31**, 713 (1976).

(40) P. H. Smit, J. L. Derissen, and F. B. van Duyneveldt, *Mol. Phys.*, **37**, 501 (1979).

(41) G. P. Arrighini, M. Maestro, and R. Moccia, *Chem. Phys. Lett.*, **1**, 242 (1967).

(42) H. J. Werner and W. Meyer, *Mol. Phys.*, **31**, 855 (1976).

(43) F. Mulder, M. C. van Hemert, P. E. S. Wormer, and A. van der Avoird, *Theor. Chim. Acta*, **46**, 39 (1977).

(44) F. Mulder, G. van Dijk, and A. van der Avoird, *Mol. Phys.*, **39**, 407 (1980).

(45) C. Møller and M. S. Plesset, *Phys. Rev.* **46**, 618 (1934).

(46) S. Diner, J. P. Malrieu, and P. Claverie, *Theor. Chim. Acta*, **8**, 390 (1967).

(47) F. Mulder and C. Huiszoon, *Mol. Phys.*, **34**, 1215 (1977).

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

	dispersion energy, kcal/mol			
			damped[c]	
	undamped[b]		ρ_m	$\rho_{8/6}$
HOH···OH$_2$	C_6R^{-6}	0.933	0.910	0.766
($R_m{}^c$ = 2.854 Å)	C_8R^{-8}	0.552	0.501	0.323
	$C_{10}R^{-10}$	0.424	0.334	0.149
	sum	1.909	1.745	1.238
			(1.661)	(0.999)
CF$_3$H···OH$_2$	C_6R^{-6}	0.624	0.608	0.446
($R_m{}^c$ = 3.580 Å)	C_6R^{-8}	0.466	0.423	0.203
	$C_{10}R^{-10}$	0.324	0.255	0.070
	sum	1.414	1.286	0.719
			(1.224)	(0.521)
CCl$_3$H···OH$_2$	C_6R^{-6}	1.418	1.383	0.651
($R_m{}^c$ = 3.651 Å)	C_8R^{-8}	1.705	1.546	0.315
	$C_{10}R^{-10}$	1.761	1.388	0.099
	sum	4.884	4.317	1.065
			(4.110)	(0.573)
c-C$_3$H$_6$···OH$_2$	C_6R^{-6}	1.032	1.006	0.663
($R_m{}^c$ = 3.562 Å)	C_8R^{-8}	0.888	0.805	0.311
	$C_{10}R^{-10}$	0.773	0.609	0.117
	sum	2.693	2.304	1.091
			(2.193)	(0.731)

[a] The $R_m{}^c$ values given in parentheses are the sums of R_m (Tables I and III) and the centers of mass displacements. [b] Calculated from the isotropic interaction coefficients of Table V. [c] Charge penetration corrections for each individual term; see text following formula 5; the damping with ρ_m (using $R_m{}^c$ for R_m) is the same for all systems, i.e., equal to the damping for H-H in $R_m{}^{H-H}$. Additionally an exchange correction has been applied to the sum of the three terms (values in parentheses) by using an overall damping function[61] $f(R) = [1 - (\rho R)^{2.326} \exp(-\rho R)]$ (R in au).

actual expression used for calculating the long-range dispersion interaction energies in the nonempirical Unsöld approach is

$$\Delta E^{\mathrm{disp}} = -\sum_{l_A,l_B=1}^{l_A+l_B\leq 4} C_{2l_A+2l_B+2}(l_A,l_B)R^{-2l_A-2l_B-2} \tag{3}$$

The interaction coefficients are given by[48,49]

$$C_{2l_A+2l_B+2}(l_Al_B) = \frac{1}{4}\,\frac{(2l_A + 2l_B)!}{(2l_A!(2l_B)!}\,\frac{\Delta_{l_A}\Delta_{l_B}}{\Delta_{l_A} + \Delta_{l_B}}\alpha_{l_A}\alpha_{l_B} \tag{4}$$

where the α_l's are static multipole polarizabilities and the Δ_l's are mean excitation energies "closely related to α_l". For more detail on the actual ab initio calculation of α_l, Δ_l, and C_n the reader is referred to ref 43, 47, and 48.

Table IV contains the calculated polarizabilities in this Unsöld approach; the table shows that the correction applied to the direct sum-over-states result is very large and that the agreement with experiment for α_1 is much better. The use of the unbalanced 4-31G* basis with its compact d functions did not improve the results for the polarizabilities of H$_2$O and c-C$_3$H$_6$, and the same is expected to be valid for CCl$_3$H and CF$_3$H. In Table V we have collected the calculated isotropic dispersion interaction coefficients in the 4-31G basis for the various possible complexes which can be formed with the molecules under study. The first four rows are of interest for this paper and show, as do the other results, the strongly increasing importance of C_8 and C_{10} for molecules of increasing size. The agreement with other ab initio results[50] in a more flexible AO basis and with accurate empirical values for C_6[51,52] is reasonable for the systems for which they are available: (H$_2$O)$_2$ and (c-C$_3$H$_6$)$_2$.

Table VII. Total Interaction Energy (ΔE), SCF Interaction Energy (ΔE^{SCF}), and Dispersion Interaction Energy (ΔE^{D}) Determined in the 4-31G Minimum of the SCF Potential Energy[a]

	$-\Delta E^b$	$-\Delta E^{\mathrm{SCF}\,b,c}$	$-\Delta E^{\mathrm{D}\,b,d}$
HOH···OH$_2$	9.41	8.08	1.33
CF$_3$H···OH$_2$	7.45	6.58	0.87
CCl$_3$H···OH$_2$	9.34	7.00	2.34
c-C$_3$H$_6$···OH$_2$	2.88	1.42	1.46

[a] See Tables I and III (geometry III) for values for R_m. [b] Energies in kcal/mol. [c] See Tables II and III (geometry III). [d] The average of the damped results for ρ_m and $\rho_{8/6}$ (values in parentheses in Table VI).

The problem which remains to be treated is the bad convergence or even divergence of the multipole expansion series, which indeed is known to be asymptotically divergent.[53,54] Table VI shows a divergence for CCl$_3$H···OH$_2$ on the minimum of the SCF potential: $C_{10}R^{-10} > C_8R^{-8} > C_6R^{-6}$ whereas for the other complexes the "convergence" is far from good. The use of a single exponential damping function[55,56] or of a truncation procedure[53,57,58] for the complete series, $\sum_n C_nR^{-n}$, looses its significance then. A way out might be to introduce different damping functions for C_6R^{-6}, C_8R^{-8}, and $C_{10}R^{-10}$, and the very little numerical information that is available (only for the small systems H···H[59] and He···He[60]) supports such an approach. Recently Thakkar and Scoles have elaborated this idea by deriving analytical expressions for the damping functions $g_n(R)$ (n = 6, 8, ···), which fit the results for H···H;[59] they are of the following form[61]

$$g_n(R) = [1 - \exp\{-2.1n^{-1}(\rho R) - 0.109n^{-1/2}(\rho R)^2\}]^n \tag{5}$$

where R is given in au and ρ is a scaling factor to account for the "size" of the interacting atoms or molecules (ρ = 1 for H···H). It has been suggested[61] to use either $\rho = \rho_m = R_m{}^{\mathrm{H\cdots H}}/R_m{}^{\mathrm{A\cdots B}}$ (R_m is the distance at the potential minimum) or $\rho = \rho_{8/6} = (C_8{}^{\mathrm{H\cdots H}}/C_6{}^{\mathrm{H\cdots H}})^{1/2}/(C_8{}^{\mathrm{A\cdots B}}/C_6{}^{\mathrm{A\cdots B}})^{1/2}$. The results for He···He[60] are well reproduced by using (5), both with ρ_m and with $\rho_{8/6}$. We have adopted this damping procedure, applying as scaling factors both $\rho_{8/6}$ and ρ_m. The large changes in the results (Table VI) show the crucial role of the scaling factor which gives rise to a dilemma as to what scaling is to be preferred. The difference is slightly exaggerated in Table VI, since our R_m values determined through ΔE^{SCF} (4-31G) are certainly too small (see section VI; for (H$_2$O)$_2$ for example, an accurate calculation[38] yields R_m = 3.0 Å): a larger R_m weakens the strong damping of Table VI with $\rho_{8/6}$, while the ρ_m damping will remain the same. Also the "convergence" of the multipole expansion will improve for a larger R_m, but R_m has to be increased by as much as 10% in order to at least remove the apparent divergent character of the series for CCl$_3$H···OH$_2$ (columns 1 and 2, Table VI). This series problem cannot be settled at present.

Finally we would like to comment on the use of the isotropic rather than the actual anisotropic dispersion energy. First of all, the dispersion energy will not be very anisotropic (compare the different components of the dipole polarizabilities) (footnote *c* of Table IV). Moreover, for the dipolar molecules its anisotropy will be overshadowed by the anisotropy of the electrostatic interactions (see, for example, ref 48). Furthermore, a check for

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(48) F. Mulder and C. Huiszoon, *Mol. Phys.*, **38**, 577 (1979). F. Mulder, Ph.D. Thesis, University of Nijmegen, The Netherlands, 1978.

(49) P. E. S. Wormer, Ph.D. Thesis, University of Nijmegen, The Netherlands, 1975.

(50) F. Mulder, G. F. Thomas, and W. J. Meath, *Mol. Phys.*, submitted for publication.

(51) G. D. Zeiss and W. J. Meath, *Mol. Phys.*, **33**, 1155 (1977).

(52) G. F. Thomas, Ph.D. Thesis, University of Western Ontario, London, Canada, 1980.

(53) D. Dalgarno and J. T. Lewis, *Proc. Phys. Soc., London, Sect. A*, **A69**, 57 (1956).

(54) R. Ahlrichs, *Theor. Chim. Acta*, **41**, 7 (1976).

(55) J. Hepburn, G. Scoles, and R. Penco, *Chem. Phys. Lett.*, **36**, 451 (1975).

(56) R. Ahlrichs, R. Penco, and G. Scholes, *Chem. Phys.*, **19**, 119 (1977).

(57) A. I. M. Rae, *Mol. Phys.*, **29**, 467 (1975).

(58) K. T. Tang and J. P. Toennies, *J. Chem. Phys.*, **66**, 1496 (1977).

(59) H. Kreek and W. J. Meath, *J. Chem. Phys.*, **50**, 2289 (1969).

(60) M. Krauss, D. B. Neumann, and W. J. Stevens, *Chem. Phys. Lett.*, **66**, 29 (1979).

(61) G. Scoles and A. J. Thakkar, private communication.

Table VIII. Calculated (4-31G) Normal Intermolecular Frequencies (cm^{-1}) for $CF_3H\cdots OH_2$ and $CCl_3H\cdots OH_2$ Complexes[a]

vibrational mode	$CF_3H\cdots OH_2$	$CCl_3H\cdots OH_2$
ν_1	52	57
ν_2	57	58
ν_3	173	174
ν_4	187	209
ν_5	316	326

[a] Water rotates in both complexes freely; i.e., the vibrational mode corresponding to the S_3 (A'') internal coordinate (cf. Figure 1) equals zero.

$CCl_3H\cdots OH_2$ showed that the orientation of the complex (Figure 1) is such that the corresponding calculated C_6 (taking into account anisotropy in both α_1 and Δ_1 in (4)[43,47] is very close to the calculated isotropic C_6 (only 1% smaller). The same will be valid for the higher dispersion interaction coefficients, since their orientational dependence is very similar to that of C_6.[47,48]

VI. Total Interaction Energy

The total interaction energies, calculated as sums of the SCF and dispersion interaction energies, are given in Table VII. The data presented in the table require some comments. (i) The 4-31G rather than 4-31G* results were used, since we believe them to be more reliable (see sections IV and V). (ii) $-\Delta E^{SCF}$ is too large and R_m is too small in such an AO basis set. This is due to a too large attractive electrostatic energy (the dipole moments are all overestimated (see Table IV), which seems to be typical for basis sets of this quality[62]) and to a too small exchange repulsion. See, for instance, ref 63). The induction energy will probably be underestimated, since the effect of too large dipole moments is completely cancelled by the too small dipole polarizabilities (the finite field SCF polarizabilities[42,64] which one should consider in this case will be too small for the same reason as the sum-over-states polarizabilities (Table IV)). Although the absolute values of ΔE^{SCF} are substantially too large, this happens in a consistent way, so their relative values can be used with more confidence (see section III). For similar reasons we have not corrected ΔE^{SCF} for the basis set superposition errors $\Delta\epsilon$. (iii) For the damped dispersion energy, $-\Delta E^D$, we have chosen to take the average of the results for ρ_m and $\rho_{8/6}$ of Table VI, corrected for both charge penetration and exchange (see discussion in Section V). The fact that $-\Delta E^D$ has been added isotropically was discussed in the previous section as being not crucial. (iv) The geometries of the complexes were optimized only on the SCF level. Indeed, the anisotropy of the dispersion energy is not expected to affect the mutual orientations significantly (see iii and section V). Furthermore, the values of R_m would probably be reduced only a little (for $(H_2O)_2$ electron correlation reduces R_m by 0.03 Å[38]) and consequently $\Delta E = \Delta E^{SCF} + \Delta E^D$ would hardly change. An exception is $c\text{-}C_3H_6\cdots OH_2$, for which the SCF potential energy curve is very flat (see section IV). The uncertainty in the damping procedure for ΔE^D makes an optimization of ΔE questionable, but if we calculate ΔE at R = 3.0 Å, following the recipe given under iii), the result is ΔE = -4.45 kcal/mol.

The results of Table VII, although not highly accurate, will be used in the thermodynamic calculations to give some theoretical insight in the possible mechanisms of anesthetic activity.

VII. The Wilson FG Analysis

Force constants for the complexes under study were evaluated on the 4-31G SCF level. It is well-known that the absolute values of the vibrational frequencies evaluated in such a basis are overestimated; as stated before, however, for our purposes the relative values are sufficient.

For $(H_2O)_2$ we have found that keeping the intramolecular coordinates fixed affects the geometry and stabilization energy of the complex only to a negligible extent (in comparison with the completely optimized dimer[34]). We have therefore taken all intermolecular modes from ref 34. Calculated frequencies of normal intermolecular modes for $CF_3H\cdots OH_2$ and $CCl_3H\cdots OH_2$ are presented in Table VIII. Let us add that water rotates in both complexes freely without energetical barrier; i.e. the vibrational mode corresponding to the $S_3(A'')$ internal coordinate (see Figure 1) vanishes.

Table IX. Thermodynamic Characteristics of the $H_2O\cdots H_2O + A \rightleftharpoons A\cdots H_2O + H_2O$ Process[a]

process	$T(R)$	ΔE, kcal/mol	$\Delta H°$, kcal/mol	$T\Delta S°$, kcal/mol	$\Delta G°$, kcal/mol	log K
$H_2O\cdots H_2O + CF_3H \rightleftharpoons$	100	1.96	1.01	−0.33	1.34	−2.92
$CF_3H\cdots H_2O + H_2O$	298		1.22	−0.60	1.82	−1.33
$H_2O\cdots H_2O + CCl_3H \rightleftharpoons$	100	0.07	−0.89	−0.53	−0.36	0.79
$CCl_3H\cdots H_2O + H_2O$	298		−0.71	−1.24	0.53	−0.39
$H_2O\cdots H_2O + c\text{-}C_3H_6 \rightleftharpoons$	100	6.53	5.16	0.72	4.44	−9.69
$c\text{-}C_3H_6\cdots H_2O + H_2O$[a]	298		5.61	3.01	2.60	−1.91
$H_2O\cdots H_2O + c\text{-}C_3H_6 \rightleftharpoons$	100	6.53	5.13	1.11	4.02	−8.77
$c\text{-}C_3H_6\cdots H_2O + H_2O$[b]	298		5.61	4.23	1.38	−1.01

[a] ΔE was calculated on the SCF (4-31G) + dispersion level (Table VII). Remaining molecular characteristics were evaluated on the SCF (4-31G) level. [b] Intermolecular vibrational frequencies for $c\text{-}C_3H_6\cdots H_2O$ chosen as 16, 19, 57, 62, and 104 cm^{-1}. [c] Intermolecular vibrational frequencies for $c\text{-}C_3H_6\cdots H_2O$ chosen as 11, 12, 38, 41, and 69 cm^{-1}.

For $c\text{-}C_3H_6\cdots OH_2$ the dispersion energy plays a relatively more important role than for the other complexes (see Table VII), and, further, its SCF potential curve is extremely flat. Hence, to calculate the harmonic force constants on the SCF level is meaningless. The vibrational frequencies for the complex, necessary for the following thermodynamic treatment, were only estimated.

VIII. Thermodynamic Treatment

The calculated characteristics of process 1 are summarized in Table IX. They were obtained by means of partition functions computed from the SCF (4-31G) and SCF (4-31G)+ dispersion constants. Rigid rotator, harmonic oscillator, and ideal gas approximations were adopted. In $CF_3H\cdots OH_2$ and $CCl_3H\cdots OH_2$ the water molecule rotates freely around the $O\cdots H$ axis; hence, the partition function for the corresponding vibrational degree of freedom was replaced by the partition function for free internal rotation.[26]

Before discussing the results of Table IX, it is necessary to make some comments on their reliability. The thermodynamic characteristics for the first two processes were evaluated theoretically on the same level of sophistication; hence, log K for those processes can be directly compared. With the third process the situation is not so straightforward. As mentioned before, for $c\text{-}C_3H_6\cdots OH_2$ we were unable to calculate the complete set of force constants. The vibrational frequencies were estimated in the following way: (i) the intermolecular stretching vibration was evaluated on the SCF 4-31G level and reduced by 20% in order to take into account the anharmonic character of the potential curve; (ii) all other frequencies were evaluated from calculated frequencies for $CF_3H\cdots OH_2$ by multiplying them by the ratio of anharmonic stretch of $c\text{-}C_3H_6\cdots OH_2$ and harmonic stretch of $CF_3H\cdots OH_2$; the resulting values are 22, 25, 76, 83, and 139 cm^{-1} (the sixth vibration is again replaced by the free internal rotation). Two different sets of frequencies were used in Table IX, by reducing these values by 25 and 50%. In order to compare the estimated values, we have collected some experimental frequencies for complexes of similar type (gas phase): $Ar\cdots ClF$ bond stretching and angle bending frequencies are[65] 47 and 41 cm^{-1}, the stretching mode of $O_2\cdots O_2$ is[66] about 24 cm^{-1}, the stretching and bending vibrations of $HF\cdots ClF$[67] are 100 and 170 cm^{-1}, the stretching

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(62) L. C. Synder, *J. Chem. Phys.*, **61**, 747 (1974).

(63) T. Wasiutynski, A. van der Avoird, and R. M. Berns, *J. Chem. Phys.*, **69**, 5288 (1978).

(64) H. D. Cohen and C. C. J. Roothaan, *J. Chem. Phys.*, **43**, 534 (1965).

(65) S. J. Harris, S. E. Novick, W. Klemperer, and W. E. Falconer, *J. Chem. Phys.*, **61**, 193 (1974).

(66) C. A. Long and G. E. Ewing, *J. Chem. Phys.*, **58**, 4824 (1973).

frequencies of $(CH_3)_2O\cdots HF$, $CH_3C_2H_5O\cdots HF$, $(C_2H_5)_2O\cdots HF$, and $(CH_3)_2O\cdots HCl$ are equal to 185, 180, 175,[68] and 120 cm^{-1}.[69] Our estimated stretching frequencies for $c\text{-}C_3H_6\cdots H_2O$ equal 83, 62, and 41 cm^{-1} (in the three sets of vibrations, see above) with the first one very probably too high. Therefore the thermodynamic characteristics for the $c\text{-}C_3H_6\cdots OH_2$ process were evaluated only with the second and third set of intermolecular vibrations.

Let us now comment on the action of CF_3H and CCl_3H (Table IX). The ΔE term, for the process under study, is positive for CF_3H and nearly zero for CCl_3H. It follows from the log K values that (i) CF_3H is unable to influence the hydrogen bond in $(H_2O)_2$ significantly either at 100 K or at 298 K and (ii) CCl_3H is able to "break" the hydrogen bond in $(H_2O)_2$. At 100 K more than 70% of the $(H_2O)_2$ originally present is converted into $CCl_3H\cdots OH_2$; this value decreases with increasing temperature, in agreement with experiment. It is about 40% at 298 K. (iii) The difference between CCl_3H and CF_3H is due mainly to the difference in $\Delta H°$.

For $c\text{-}C_3H_6$ (Table IX) ΔE and also $\Delta H°$ are highly positive. In itself this $\Delta H°$ value would suggest that $c\text{-}C_3H_6$ cannot break the hydrogen bond in the water dimer. It turns out, however, that the entropy term can compensate for the unfavorable enthalpy value, especially at higher temperatures. It has been pointed out above that the determination of the energy of stabilization for the $c\text{-}C_3H_6\cdots OH_2$ system is rather uncertain. Optimizing ΔE instead of ΔE^{SCF} yields an energy of stabilization of −4.45 kcal/mol. If the thermodynamic calculation is performed with this ΔE, 1.03 and −0.19 kcal/mol are obtained for $\Delta G°$ at 298 K. Since the intermolecular vibration frequencies for $c\text{-}C_3H_6\cdots OH_2$ are only estimated, a direct comparison of the log K values for this and the other processes is not warranted.

It is important to note at this point that any increase in the contributions from the higher dispersion coefficients (C_8, C_{10}) (for instance by applying another scaling procedure) would favor the formation of the mixed complex over the water–water complex. Thus from the point of view of the mixed complex formation (that is anesthetic action) our calculations are on the "pessimistic" side.

Our aim is only to demonstrate that small positive or even negative $\Delta G°$ values could be reached not only by negative $\Delta H°$ but also by positive $\Delta H°$ if accompanied by a positive $T\Delta S°$. The following conclusions can be made on the basis of the log K values: (i) at 100 K there is no chance that $c\text{-}C_3H_6$ breaks the hydrogen bond in $(H_2O)_2$; (ii) at 298 K the probability of this increases significantly; (iii) the ability of $c\text{-}C_3H_6$ to perturb the hydrogen bond is to be ascribed to rather large positive $T\Delta S°$ values (in contrast with CCl_3H where $T\Delta S°$ is negative).

IX. Conclusion

The thermodynamic equilibrium between a water dimer on the one hand and chloroform, fluoroform, and cyclopropane on the other hand has been examined by quantum chemical methods. While the calculations are necessarily approximate, the trends appear clearly. In the case of chloroform, a potent anesthetic, the equilibrium clearly favors the formation of the mixed dimer at 100 K. At 298 K about 40% of the originally present hydrogen-bonded $(H_2O)_2$ is converted into $CCl_3\cdots OH_2$. This implies "breaking" the hydrogen bond ($O\text{–}H\cdots O$) in many of the water dimers and formation of a new $C\text{–}H\cdots O$-type hydrogen bond. This is just what has been predicted on the ground of our spectroscopic results[9,10,14,15,18-20] and substantiates the contention that polar interactions like the breaking and formation of hydrogen bonds are important for the mechanism of general anesthesia. It is equally satisfactory in this respect that in the case of fluoroform which has no anesthetic potency the equilibrium turns out to be in favor of the water–water dimer, not the mixed dimer. Our calculations also substantiate the importance of nonpolar (dispersion) interactions. Our results on cyclopropane show that even a nonpolar hydrocarbon anesthetic might ≤break" the hydrogen bond in the water dimer. $\Delta G°$ can have small positive or even negative values (favoring the mixed dimer) not only if $\Delta H°$ is negative but also if $T\Delta S°$ is positive with a positive $\Delta H°$. Naturally, the water dimer is not a model for a cell membrane. However, water–water and other $O\text{–}H\cdots O$-type hydrogen bonds are plentiful inside and around the membrane and certainly make a contribution to the stability of its lipids and proteins whereby influencing the permeability of the membrane.

Both polar and nonpolar interactions must be important for the mechanism of anesthesia.

In forthcoming papers the interaction of anesthetics with other types of hydrogen bonds will be examined.

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(67) S. E. Novick, K. C. Janda, and W. Klemperer, *J. Chem. Phys.*, **65**, 5115 (1976).

(68) R. K. Thomas, *Proc. R. Soc. London, Ser. A*, **A322**, 137 (1971).

(69) J. E. Bertie and M. V. Falk, *Can. J. Chem.*, **51**, 1713 (1973).