10-Benzyl-*N,N*-dimethyl-9-carboxamidoacridan (3). To a solution of *N,N*-dimethyl-9-carboxamidoacridan (0.5 g, 20 mmol) in 30 ml of 50% methanol, sodium bicarbonate (0.17 g, 20 mmol) and benzyl chloride (0.5 g, 35 mmol) were added. The solution was refluxed for 4 hr. Hot water (40 ml) was then added and the colorless crystals were separated by filtration after cooling to room temperature (0.5 g, 80%): mp 172–175°. *Anal.* ($C_{23}H_{23}N_2O$) C, H, N.

9-Methyl-10-benzyl-*N,N*-dimethyl-9-carboxamidoacridan (5). Freshly cut lithium metal (0.45 g, 65 mmol) was added to 100 ml of anhydrous ether under nitrogen. After cooling to −10°, *n*-butyl bromide (4.4 g, 30 mmol) in 20 ml of ether was added dropwise over 30 min and the mixture was stirred until most of the metal was dissolved. The solution was quickly filtered to remove the unreacted metal and chilled to −30 to −40°. A solution of 10-benzyl-*N,N*-dimethyl-9-carboxamidoacridan (3.0 g, 9 mmol) in 250 ml of anhydrous ether was added dropwise over 30 min. The stirring was continued for 1 hr below −30°. Excess methyl iodide (5 ml) in 20 ml of ether was then added to the pale green solution and the mixture was stirred for 30 min. The solvent was removed by distillation at room temperature and reduced pressure. After the addition of water (50 ml) the mixture was extracted with chloroform. The product was obtained after removal of chloroform and recrystallization from ethanol (4.2 g, 85%): mp 234–238°. *Anal.* ($C_{24}H_{24}N_2O$) C, H, N.

9-Methyl-*N,N*-dimethyl-9-carboxamidoacridan (6). A solution of 10-benzyl-9-methyl-*N,N*-dimethyl-9-carboxamidoacridan (0.5 g, 20 mmol) in 95% ethanol and 48% hydrobromic acid (1:1, total volume 10 ml) was hydrogenated after the addition of palladium on charcoal as the catalyst (0.1 g) at 2.7 atm (2.76×10^5 N m^{-2}). After 20 hr the catalyst was removed by filtration and the filtrate neutralized by sodium bicarbonate. The product was obtained after the removal of the solvent from the chloroform extract followed by recrystallization from methanol (0.25 g, 45%): mp 166–170°. *Anal.* ($C_{17}H_{18}N_2O$) C, H, N.

10-Methyl-*N,N*-dimethyl-9-carboxamidoacridan (2). The methosulfate 8 was dissolved in ethanol (4.1 g in 100 ml) and subjected to hydrogenation at 2.7 atm in the presence of Raney nickel. The reduction was complete in 5 hr as indicated by the loss of green coloration. After filtration the solution was concentrated to 25 ml and then diluted to 50 ml by the addition of water. The product separated as a white solid (2.8 g, 95%) which was recrystallized from 75% ethanol as colorless needles, mp 122–123°. *Anal.* ($C_{17}H_{18}N_2O$) C, H, N.

***N,N*-Dimethyl-9-carboxamido-10-benzylacridinium Chloride (9).** A solution of *N,N*-dimethyl-9-carboxamidoacridine (0.8 g, 32 mmol) in 5 ml of 95% ethanol was refluxed with benzyl chloride (1 g, 80 mmol) for 5 hr. After removal of ethanol by distillation under reduced pressure a yellow solid was obtained. This product was washed with toluene and ether and was utilized for further reactions without recrystallization: mp 215–220°.

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Hydrogen Bond Breaking Potency of Fluorocarbon Anesthetics

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It can be shown by infrared spectroscopy that fluorocarbons containing chlorine, bromine, or iodine can open N–H---N, O–H---O, N–H---O=C type hydrogen bonds in solutions. This is probably achieved by a competitive mechanism of association consisting in the formation of donor-acceptor complexes. There is a striking parallelism between the hydrogen bond breaking ability and the anesthetic potency of these compounds.

It has been noticed in the course of investigations carried out in this laboratory on the anharmonicity of vibrations in hydrogen bond systems that bromine-containing fluorocarbons hinder the formation of hydrogen bonds.[1] Our first observations were made on 1,2-dibromotetrafluoroethane (CF_2BrCF_2Br; also known as fluorocarbon or freon 114B2). This compound acts as a hydrogen bond breaker. In our first experiments the solvent was a 1:1 mixture of CCl_3F (fluorocarbon or freon 11) and CF_2BrCF_2Br and the hydrogen bonds were of the N–H---N type formed by the self-association of secondary amines.[2] This solvent can be used down to liquid nitrogen temperature. It becomes a glass at about −140°. As temperature was lowered the intensity of the free (unassociated) NH stretching band increased while the intensity of the stretching band of the hydrogen bonded NH group decreased and disappeared completely at −190°. This is a striking phenomenon and it is the exact opposite of what might have been expected. It is due to CF_2BrCF_2Br; when we used a solvent containing CCl_3F and methylcyclohexane but no CF_2BrCF_2Br we observed the normal increase in the intensity of the associated band and the simultaneous decrease in the intensity of the free band when temperature was lowered. Similar observations were made in the case of self-associated aromatic amines.[3] In the case of stronger hydrogen bonds like in pyrrole,[4] alcohols, phenols,[1] or amides[5] instead of the decrease of the intensity of the associated band we observed a slower increase in

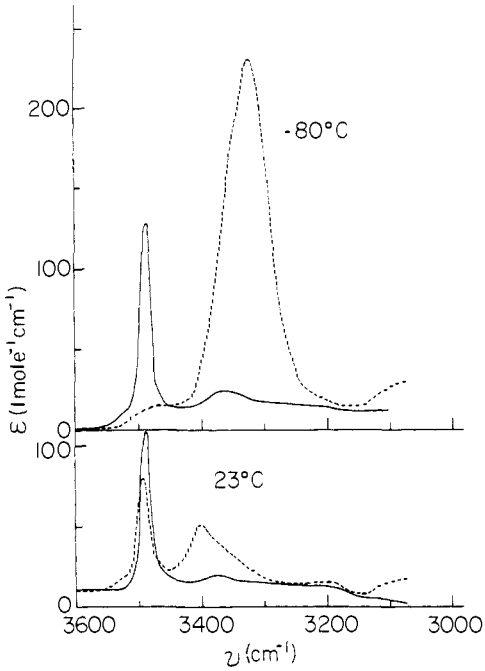

Figure 1. The NH stretching region of the infrared spectrum of a 0.048 M solution of N-methylpivalamide in a 1:1 mixture of CCl_3F and halothane (——) and in a 1:1 mixture of CCl_3F and methylcyclohexane (- - -): (a) at 23°; (b) at −80°.

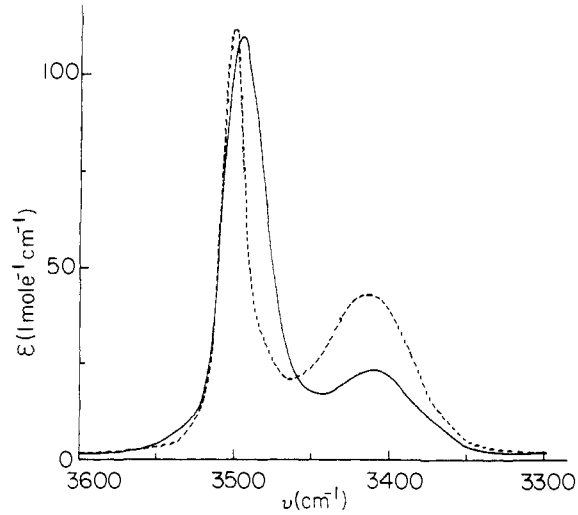

Figure 2. The NH stretching region of the infrared spectrum of pyrrole at room temperature: (a) in a 0.54 M solution in CCl_3F (- - -); (b) in a 0.57 M solution in halothane (——).

the intensity of that band as temperature was lowered. We interpreted these phenomena in terms of a competitive mechanism of association, probably by donor-acceptor complex formation involving the N or O lone pairs and the C-Br links. (Association by hydrogen bonds will not be considered as a donor-acceptor complex formation in this paper.)

Now, chlorine-, bromine-, and iodine-containing fluorocarbons are known to have anesthetic potency and one of them, halothane ($CF_3CHClBr$), is the most widely used inhalation anesthetic. If this is so, it is natural to ask if there is a connection between the hydrogen bond breaking and the anesthetic potencies of these molecules.

The importance of the above observations might be even more general, however. Competition between association by hydrogen bonding and by donor-acceptor complex formation might be a device used by the living organism to open and close hydrogen bonds. These might be

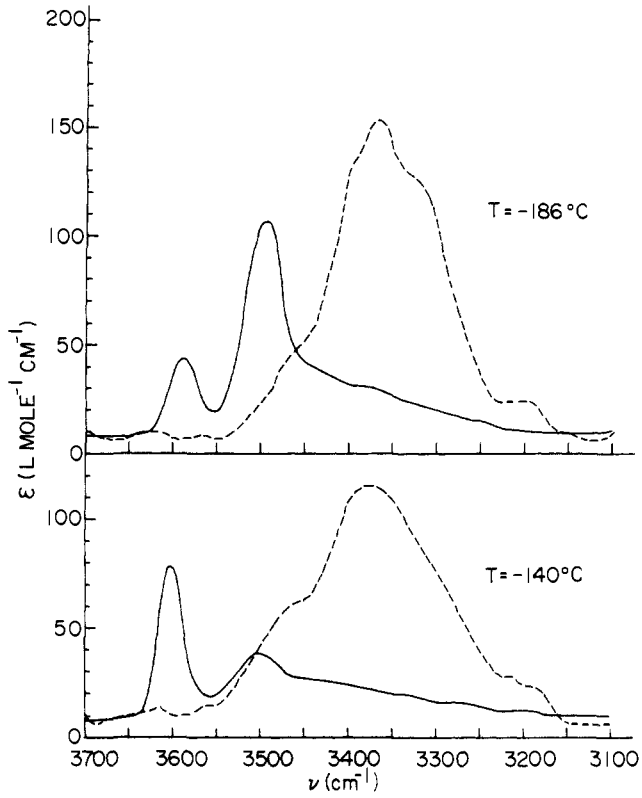

Figure 3. The OH stretching region of the infrared spectrum of 2,6-diisopropylphenol at −140 and −186°: 0.13 M in a 1:1 mixture of CCl_3F and methylcyclohexane (- - -) and in a 1:1 mixture of CCl_3F and halothane (——).

water-water bonds, or water-protein or water-nucleic acid bonds, or N-H---N and N-H---O type hydrogen bonds holding the double helices together. Their opening and closing might affect the conformations of proteins or nucleic acids and thus the passing of messages through the nervous system. It might affect cell division; it has been indeed observed that halothane is able to arrest mitosis.[6]

In view of these considerations an extensive program of research has been initiated in this laboratory in search of a relation between anesthetic potency and hydrogen bond breaking ability of fluorocarbons. As is stated below, a striking parallelism has been found.

Results

The hydrogen bond systems which have been studied were self-associated diethylamine, pyrrole, indole, 2,2,4-trimethyl-3-pentanol, *tert*-butyl alcohol, 2,6-diisopropylphenol, N-ethylacetamide, N-methylpivalamide, δ-valerolactam, acetanilide, N-methylbenzamide, and propane-1-thiol. Their spectra were taken in solutions containing one of the following fluorocarbons: CCl_3F, CF_3CCl_2H, n-C_3F_7Br, CF_2Br_2, CF_2BrCF_2Br, $CF_3CClBrH$ (halothane), $CF_2BrCClFH$, n-C_3F_7I, i-C_3F_7I, CF_2BrCF_2I.

The infrared spectra were measured on a Perkin-Elmer Model 621 spectrometer with techniques described in our previous publications. The samples were highly purified products from the E. I. du Pont de Nemours Co. or the Peninsular Chemical Research Corp. and were further purified by distillation.

A detailed description of these spectra will be given in a more extensive publication; here the main points will be illustrated on typical examples.

Figure 1 shows the spectrum of a dilute solution of N-methylpivalamide (N,2,2-trimethylpropionamide) in a 1:1 mixture of CCl_3F (freon 11) and halothane and in a 1:1 mixture of CCl_3F and methylcyclohexane at +23 and at

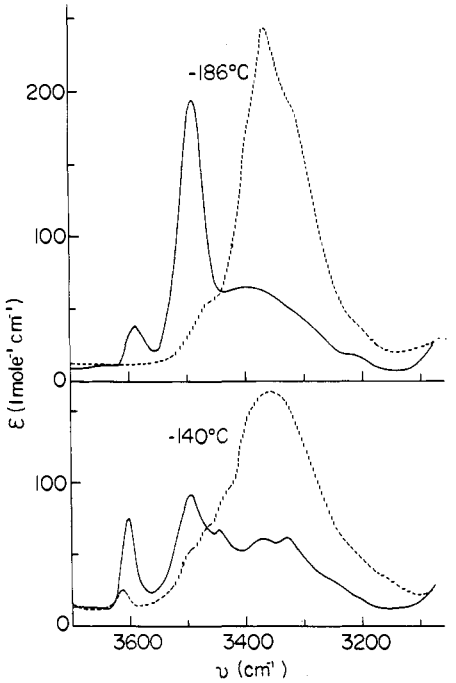

Figure 4. The OH stretching region of the infrared spectrum of 2,6-diisopropylphenol at −140 and −186°: 0.054 *M* in a 1:1 mixture of CCl_3F and methylcyclohexane (- - -) and in the same solution but with 1.1 *M* CF_3CHCl_2 added (——).

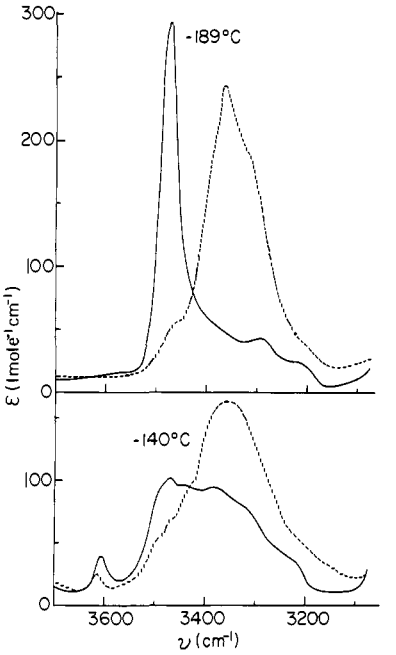

Figure 5. The OH stretching region of the infrared spectrum of 2,6-diisopropylphenol at −140 and −186°: 0.049 *M* in a 1:1 mixture of CCl_3F and methylcyclohexane (- - -) and in the same solution but with 0.46 *M* n-C_3F_7I added (——).

−80°. At +23° the difference between the two spectra is already quite evident; the associated band near 3400 cm^{-1} (which corresponds to the N-H---O=C< type hydrogen bond is this case) is much weaker and the free band is stronger in the halothane containing solvent. At −80° the effect takes dramatic proportions; while as expected, the free band disappears and the associated band becomes very intense in CCl_3F + methylcyclohexane the opposite is the case in CCl_3F + halothane.

Figure 2 shows the case of pyrrole at room temperature. This time a solution in pure CCl_3F is compared to a solution in pure halothane. The same observation is made as in the case represented by Figure 1; the associated band is much weaker in halothane.

The other figures show the spectra of self-associated 2,6-diisopropylphenol (DIPP) at low temperatures (−186, −140°). The role of low temperature in these experiments is to magnify the effects by promoting association so that they can be examined and illustrated better. The forming or opening of hydrogen bonds proceeds gradually with temperature and the phenomenon which we are describing is always present even at room temperature. Figure 3 compares the spectrum of DIPP in CCl_3F + methylcyclohexane and in CCl_3F + halothane. While in the former the broad associated (so-called polymer) band is preponderant, in the halothane-containing solvent the most intense band (at 3490 cm^{-1}) is an oligomer band due to a less associated species (perhaps a dimer) and even the free band is seen (at −186°) near 3590 cm^{-1}.

It is natural to ask if the presence of the bromine atom is a necessary condition for the obtention of this hydrogen bond breaking. We tried several fluorocarbons containing only chlorine and fluorine. The changes we have observed in the spectrum with respect to those taken in purely hydrocarbon solvents pointed in the direction of less association in the chlorofluorocarbons but they were slight. However, if the molecule contains a hydrogen atom in addition to fluorine and chlorine, the effect becomes much stronger, as strong as with the brominated molecules. Figure 4 compares DIPP in CCl_3F + methylcyclohexane and DIPP

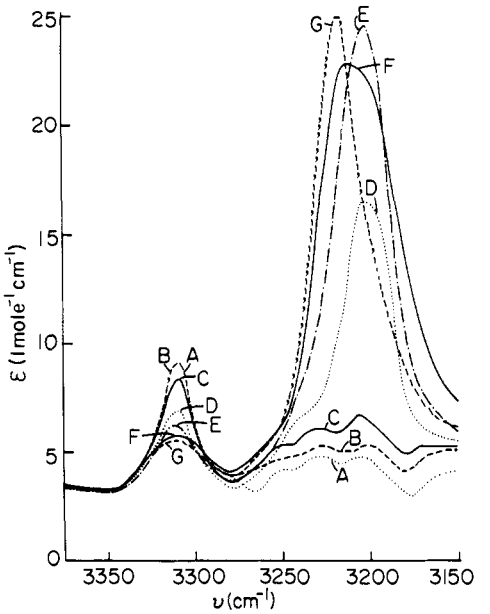

Figure 6. The infrared spectra of 0.6 *M* solution of diethylamine in a 1:1 mixture of CCl_3F and methylcyclohexane (FM) at −190° in the presence of variable amounts of C_3F_7Br. Concentration of C_3F_7Br: A, 1.04 *M*; B, 0.87 *M*; C, 0.62 *M*; D, 0.42 *M*; E, 0.32 *M*; F, 0.08 *M*; G, 0.

in the same solvent to which about 1.0 *M* of CF_3CHCl_2 has been added. The change is striking! This latter molecule is about as good a hydrogen bond breaker as halothane.

In Figure 5 the hydrogen bond breaker is an iodine-containing molecule, n-C_3F_7I. Again the oligomer band replaces the polymer band when it is added to the solution; indeed, it is even more intense than for halothane or CF_3CHCl_2. The free band is not observed at −186° but the oligomer band is extremely intense showing the dissociation of most hydrogen bonds of the polymer.

A further observation can be made on the N-H---N type hydrogen bonds of secondary amines. Figure 6 shows the results of a concentration study on a 0.6 *M* solution of di-

ethylamine carried out at −190°. In a 1:1 mixture of CCl_3F and methylcyclohexane, that is, with no bromine in the solution, we find a weak free NH band at 3308 cm^{-1} and a much stronger associated band at 3214 cm^{-1} (curve G). If we add 0.08 *M* of C_3F_7Br to the solution the associated band becomes broader and undergoes a shift to lower frequencies. The band is obviously a complex band. When we increase the proportion of C_3F_7Br to about 0.32 *M* the peak appears at 3202 cm^{-1} (curve E). It is clear from the comparison of these three curves that the first result of the perturbation by C_3F_7Br is the formation of a weak aggregate to which the peak of curve E is related and that curve F contains comparable amounts of both the bromine-unperturbed species and this aggregate. This aggregate is likely to be the dimer containing the N-H---N type hydrogen bond with an additional solvent perturbation by the bromine-containing molecule. The formation of N-H---Br type hydrogen bonds is considered unlikely since the corresponding N-H band would be expected to have a higher frequency (perhaps 3250–3270 cm^{-1}), but this possibility is not entirely ruled out. Anyway, the main result is that at higher C_3F_7Br concentrations (curves D, C, B, and A) the intensity of this band decreases rapidly and when C_3F_7Br and diethylamine are at about the same concentration only weak associated bands remain and at the same time the free NH band increased in intensity and became the only prominent NH band in the spectrum. It is seen that the aggregate which was the first result of the perturbation was destroyed at higher C_3F_7Br concentrations and that the new complex is *not* a hydrogen-bonded adduct and that is essentially a 1:1 complex (see Discussion). Similar observations were made with CF_2BrCF_2Br and CF_2Br_2.

From the whole body of our results on the systems mentioned in the introduction, the following general observations could be made. (1) Perfluorinated molecules have no hydrogen bond breaking potency. (2) Fluorocarbons containing only chlorine in addition to carbon and fluorine have only a weak effect. (3) Bromine- and iodine-containing fluorocarbons are strong hydrogen bond breakers and for fluorocarbons containing no hydrogen the order of increasing hydrogen bond breaking potency is Cl < Br < I. (4) Chlorine-containing fluorocarbons become strong hydrogen bond breakers if they contain a hydrogen atom. (For example, $CF_3CCl_3 \ll CF_3CHCl_2$.)

Bromine-containing fluorocarbons also become stronger hydrogen bond breakers if they contain a hydrogen atom. The case of the iodides is more complicated in this respect.

Table I illustrates the trends on the examples of 2,6-diisopropylphenol and pyrrole. The *apparent* molecular extinction coefficients of the associated band (the "polymer" band) computed with the overall initial concentration (which is not equal to the concentration of any given associated species) are multiplied by the concentration of the fluorocarbon which was added to the solution and acted as a hydrogen bond breaker. This is considered as a rough measure of the hydrogen bond breaking potency of the different fluorocarbons for one given hydrogen-bonded system at a given temperature. There is much to be said about this procedure and the numbers in Table I do not pretend to any degree of accuracy. The trend appears clearly, however.

Table I. Approximate Hydrogen Bond Breaking Potency (HBBP) for 2,6-Diisopropylphenol and for Pyrrole[a]

Fluorocarbon	HBBP, 2,6-diisopropylphenol	Fluorocarbon	HBBP, pyrrole
i-C_3F_7I	10	*n*-C_3F_7I	50
n-C_3F_7I	20	$CF_3CHClBr$	250
CF_2BrCF_2I	20	CF_3CHCl_2	250
$CF_3CHClBr$ (halothane)	60	$CF_2BrCHFCl$	400
CF_3CHCl_2	60	CF_2BrCF_2Br	1100
n-C_3F_7Br	90	CCl_3F	1900
CCl_3F	1000		

[a] The data were taken from spectra measured at −186 (for 2,6-diisopropylphenol) and −140° (for pyrrole) in a 1:1 mixture of CCl_3F and methylcyclohexane except for CCl_3F itself which was taken in a purely hydrocarbon solvent. HBBP is the product of the apparent molecular extinction coefficient of the "polymer" OH stretching band and the fluorocarbon concentration (see text).

Discussion

Until recently theories of anesthesia centered around the clathrate hydrate theory of Pauling[7] and Miller[8] or the correlation between lipid solubility and anesthetic potency.[9] In a recent review Seeman[10] gave a comprehensive account on the latter aspect and the membrane actions of anesthetics. However, as has been recently pointed out by Mullins[11] neither the clathrate hydrate nor the lipid solubility idea amounts to a proposal for the mechanism of anesthesia.

Significant developments seem to have occurred in the last 2 years. Nunn[12] drew attention to the specificity of action of inhalation anesthetics at the cellular level and put forward the idea that "... in some cases, binding between anesthetics and proteins can produce conformational changes sufficient to alter their properties." Ueda and Kamaya[13] studied the mechanism of anesthesia using firefly luminescence as a model system. They came to the conclusion that anesthetics act at a hydrophobic site of the enzyme luciferase inducing a change thereby the original "folded" enzyme becomes "unfolded." Eyring, *et al.*,[14] after a thorough discussion of the thermodynamical and structural aspects of the observations made by Ueda and Kamaya suggest that "... anesthetic molecules combine with hydrophobic regions of protein or proteins essential to the maintenance of consciousness, thereby causing a conformational change to a less active or an inactive form."

Well, the "action at a hydrophobic site" might well be a donor–acceptor complex formation or a perturbation leading to it and it might be followed by the breaking of vital hydrogen bonds. At any rate, our results strongly suggest that an important step in the action of fluorocarbon anesthetics consists in the breaking or weakening of hydrogen bonds.

To substantiate this contention we can cite the works of Krantz and Rudo,[15] Larsen,[16] and Clayton[17] on the relative anesthetic potency of fluorocarbons. Summarizing their extensive studies involving a very great number of fluorocarbons Krantz and Rudo stated that "Halogenation of hydrocarbons and ethers increases potency in the following order: F < Cl < Br < I. One or more hydrogen atoms in the molecule are necessary for effective central nervous system depression. Complete hydrogen substitution by fluorine usually produces a physiologically inert compound." Similar conclusions can be drawn from the data of Larsen and Clayton. (See, in particular, Larsen's Table VII.)

All this is in excellent qualitative agreement with our results on the hydrogen bond breaking potency of fluorocarbons as stated above. There exists a striking parallelism between the anesthetic potency and the hydrogen bond breaking ability of fluorocarbon anesthetics.

Table II. Lowest Vertical Ionization Potential (in eV) of Some Fluorocarbons Determined by Photoelectron Spectroscopy Using a Perkin-Elmer PS-16 Instrument

Compound	Lowest Cl, Br, or I lone pair IP, eV	Ref
CF_3Cl	13.0	25
C_2F_5Cl	13.0	*a*
CF_3Br	12.0	25
C_2F_5Br	12.0	*b*
n-C_3F_7Br	12.0	*b*
CF_3I	10.8	*c*
C_2F_5I	10.7	*c*
n-C_3F_7I	10.6	*c*
CF_2HCl	12.6	25
CF_2BrCl	11.8	*d*
$CF_2BrCFClH$	11.7	*b*
$CF_3CClBrH$ (halothane)	11.2	*e*
CF_2Cl_2	12.3	25
CF_2Br_2	11.2	*d*
$CFHCl_2$	12.0	25
CF_2BrCF_2Br	11.4	*b*

[a] J. Doucet, P. Sauvageau, and C. Sandorfy, in press. [b] R. Routhier, P. Sauvageau, and C. Sandorfy, unpublished results. [c] R. A. Boschi and D. R. Salahub, *Mol. Phys.*, in press. [d] J. Doucet, R. Gilbert, P. Sauvageau, and C. Sandorfy, in press. [e] D. W. Turner, C. Baker, A. D. Baker, and C. R. Brundle, "Molecular Photoelectron Spectroscopy," Wiley-Interscience, London, 1970, p 242.

At present we are accumulating data in our laboratory in an attempt to establish a quantitative relationship although such a relationship must not necessarily exist. For the purposes of this preliminary account we are restraining ourselves to establishing the loose relationship outlined above.

One might object that the conditions under which our spectra were obtained are very far from *in vivo* conditions. However, the hydrogen bonds we have studied are very similar to those which the living organism uses most. The alcohol-alcohol or phenol-phenol bonds resemble closely the water-water bonds. N-H---N type bonds are also widespread and the N-H---O=C bond of the amides is actually one of the most important types of hydrogen bond occurring in the organism.

At this point we should like to comment on the possible nature of the complex whose formation provides the competitive mechanism leading to breaking of hydrogen bonds. Since hydrogen bonds of the type which exists in the systems which we were studying have energies (ΔH values) of the order of 2-6 kcal/mol, the likely competitors are donor-acceptor complexes. From the ionization potentials we can infer that the Cl-, Br-, or I-containing fluorocarbons act as electron acceptors and the amines, alcohols, phenols, and thiols as electron donors.

The lowest ionization potentials of diethylamine,[18] pyrrole,[19] aliphatic alcohols,[20] and phenol[21] are near 8.0, 8.2, 10.5, and 8.75 eV, respectively, while the lowest IP's of the chlorine- or bromine-containing fluorocarbons which were used in our studies are always higher than 11 eV (Table II). (In certain cases this may not be so for iodides which present some special problems to be treated in a separate publication.) The lowest IP of amines and alcohols corresponds to the taking out of an electron from the essentially nonbonding N or O lone-pair orbital. In the case of phenol, pyrrole, and indole the frontier orbital is probably of the π type.[22] At any rate our electron donors in the complexes which are formed are of the "bπ" (bonding π) type according to the nomenclature established by Mulliken and Person.[23] The electron-acceptor orbital would then be an antibonding (excited) σ orbital, "aσ", since these molecules do not possess vacant orbitals. The energies of these excited orbitals are high; they are about 6 eV above the ground state for the bromides, 7-8 eV for the chlorides,[24,25] and 5-6 eV for the iodides[26] as is known from the ultraviolet spectra.

A perhaps more likely hypothesis is the formation of contact complexes in which the electron-attracting site is the fractional positive charge on the Cl, Br, or I atoms due to the strong electron pull of the fluorine atoms (*cf.* ref 27). Actually, the hydrogen bond breaking potency of our fluorocarbons runs parallel with their lowest IP which is always due to ionization from a lone-pair orbital of the highest halogen.[25] In Table II we collected a few of these ionization potentials to illustrate this point. Only molecules with the same number of (nonfluorine) identical halogens should be compared since in the presence of more than one the interaction of their lone-pair atomic orbitals creates several molecular orbitals built of lone-pair AO's.

A remark should be made on the nature of the initial perturbation which has been observed with the aliphatic secondary amines. Let us consider a hydrogen bond dimer

$$\bar{N}_1\text{-H---}\bar{N}_2\text{-H}$$

If the halogen (X) attacks at the N_1 lone pair, the result is expected to be $-Br^-:{}^+N\text{-H—N-H}$ with some *increase* in the energy of the hydrogen bond. This might be the reason for the lowering of the N-H frequency following this initial perturbation which has been mentioned above. If, however, the attack takes place on the lone pair of N_2 which is a proton acceptor, the weakening and eventual dissociation of the hydrogen bond must follow. How often these two events occur will depend on the availability of free $\bar{N}$ sites and the overall and local concentration of the fluorocarbon. According to these conditions certain hydrogen bonds might be only perturbed, others will be broken.

It follows from this discussion that donor-acceptor complex formation and hydrogen bond breaking are connected and that it is just as logical to relate anesthetic action to complex formation as to hydrogen bond breaking ability. The direct evidence we have presented is related to the latter, however.

There are, of course, inhalation anesthetics which are not fluorocarbons. These are currently examined in our laboratory in the same context. It is not pretended, however, at this stage that these too exert their action by the same mechanism.

Conclusions

Infrared spectroscopic measurements give evidence that fluorocarbon anesthetics break hydrogen bonds in solution probably by means of a competitive mechanism of association by donor-acceptor complex formation. These hydrogen bonds are similar to those occurring in the living organism. There is a well-pronounced parallelism between the hydrogen bond breaking ability and the anesthetic potency of these molecules. Both potencies increase in the order F < Cl < Br < I and the presence of a hydrogen atom in the molecule further increases it. These observations lead to the suggestion that the breaking or perturbing of hydrogen bonds is an important step in the mechanism of action of fluorocarbon anesthetics.

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A Theoretical Approach to Structure–Activity Relationships of Chloramphenicol and Congeners

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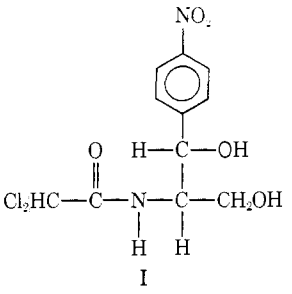
In this study the most stable conformation of the chloramphenicol molecule was calculated by means of extended Hückel theory and found to agree with nmr data. Based on those conformational results a three-dimensional picture of the possible binding sites of the molecule to a receptor is displayed. The influence of substitution at the phenyl ring and the acylamino side chain on the biological activity of the chloramphenicol molecule has been investigated by CNDO/2 and model interaction calculations. An explanation of the influence of the para-substituted phenyl ring of chloramphenicol is presented.

Many studies have been made on the structure-activity relationships of the chloramphenicol molecule, I, which are of interest due to its important antibacterial action.



I

The pharmacological evaluations of numerous congeners of the natural molecule have revealed that apparently three parts of the molecule are specifically involved in drug–receptor events. The propanediol moiety critically determines the activity,[1] since changes at this part of the molecule, like replacement[2] or acetylation[3,4] of the hydroxyl groups or extension of the 3-carbon chain,[5,6] result in a complete loss of antibiotic activity. The other two features, the para substituent at the benzene ring and the dichloromethyl group at the acylamino side chain, have been the subject of several chemical modifications.[7,8] Recently the first substance has been described, which exerts a higher antibacterial activity than the mother substance.[9] This modification possesses a trifluoromethyl group instead of the dichloromethyl group at the acylamino side chain. There are several other congeners in this series known, with a broad range of activity.[7,10] Besides the dichloromethyl group, the *p*-nitro substituent has been found to be replacable with a variety of groups or atoms,[7,11] but all of them are lower in activity. Efforts have been made to retain activity by replacing the phenyl ring with other aromatic systems, but there has been little success. Only the nitrothienyl congener retains some antibiotic activity.[12,13]

Despite the fact that much has been accomplished, there is still considerable uncertainty concerning the drug–receptor interactions. In this study we try to derive further information which might help to elucidate these events by means of theoretical methods.

Molecular Conformation. The confirmation of chloramphenicol has been previously studied by nmr and Raman spectroscopy[14] and more recently by ORD and