Conformational Analysis of Acridan Derivatives by Nuclear Magnetic Resonance Spectroscopy. A Relationship between Conformation and Pharmacological Activity

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Six acridan derivatives with an N,N-dimethylcarboxamide group in the 9 position as a common structural feature and a methyl and/or benzyl group in 9 and 10 positions were synthesized and their proton magnetic resonance spectra were studied in chloroform at various temperatures. From the free energies of activation for the rotation around the CO-N amide bond and the chemical shifts of the amide methyl protons, certain conclusions were drawn regarding the conformational changes caused by the methyl and benzyl groups. With two bulky groups (amide and methyl) in the 9 position, the acridan system approaches a planar time-average structure. With one large group (amide) in the 9 position, another large group (methyl and benzyl) in the 10 position causes the conformation of the central six-membered ring to favor a highly puckered boat conformation. These results, when applied to the 9-aminoalkyl derivatives of acridan, may help in achieving a better understanding of the conformation-activity relationship of the psychotropic agents related to clomacran.

An important group of compounds exhibiting psychotropic activity (CNS stimulant and depressant) comprises a number of tricyclic derivatives (6-6-6 compounds) with the central six-membered ring bearing an aminoalkyl side chain. As a class they present an interesting case to a medicinal chemist interested in structure-activity relationships. In many cases a simple structural modification in the central ring is known to cause a rather dramatic change in the activity. Zirkle and Kaiser have recently drawn attention to the structural features associated with the CNS activity of some acridan derivatives.¹ Methyl substitution at 9 and 10 positions can affect profoundly the activity of these acridans. Of the 9-aminoalkylated derivatives, clomacran (I) has approximately the same neuroleptic potency as chlorpromazine. Introduction of a methyl substituent in the 10 position of clomacran enhances the CNS-depressant activity slightly; however, 9methyl substitution abolishes this activity. In 10-aminoalkyl series II, an acridan with no methyl group in the 9 position, has chlorpromazine-like neuroleptic potency while dimethacrin (III), an acridan with two methyl groups in the 9 position, has the opposite imipramine-like antidepressant activity.1 Although the mechanism of ac-



tion of the psychotropic agents is not clearly understood at the molecular level, numerous observations indicate that at least some of the pharmacological effects might be due to interference caused by these agents with the actions of norepinephrine and dopamine.² Zirkle and Kaiser postulate that the substitution of a hydrogen atom by a methyl group in the 9 position causes a change in the conformation of the ring system which might prevent a part of the system from attaining a conformation suitable for interaction with "a planar surface" at the active site.¹ According to these authors this change in the conformation may then be responsible for the loss of neuroleptic potency and introduction of antidepressive actions.

The precise role played by the methyl groups in 9 and 10 positions toward affecting the conformational features of the acridan nucleus is not clear. In the present study we have investigated the conformational influences of methyl and benzyl substituents at these positions by synthesizing a number of acridan derivatives (1-6) and studying their



proton magnetic resonance spectra in solution. The common structural feature of these acridans is the N, N-dimethylcarboxamido group in the 9 position. We chose to work with the acridans with the amide function rather than the aminoalkyl function (present in the CNS-active derivatives of acridan) after realizing the complexities in the pmr spectra of the latter group. Moreover, in a previous publication we had observed an abnormally large chemical shift difference between the methyl protons of the dimethylcarboxamido group in N,N-dimethyl-9-carboxamido-9,10-dimethylacridan (4).³ In the present study, the information regarding the conformational features of these molecules (1-6) is derived mainly from the characteristics of the methyl groups belonging to the N,N-dimethylcarboxamido moiety in the 9 position. These characteristics, studied by variable temperature pmr spectroscopy, are the free energies of activation for the rotation around the CO-N bond and the chemical shifts of these amide methyl protons. The changes in these parameters are attributed to the conformational changes of the acridan ring system caused by the substituents in 9 and 10 positions.

Results and Discussion

The pmr data for the 9-acridan amides (1-6) are shown in Table I. The chemical shifts of the two amide methyl protons are represented by δ_1 and δ_2 . These were determined at temperatures sufficiently below the coalescence temperatures and are indicative of the maximum separation between the two signals $(\Delta \delta_{max})$. The coalescence temperature $T_{\rm C}$, the lowest temperature when a single hy-

Table I. Pmr Data for Amides $RCON(CH_3)_2$ (0.5 *M* Solutions in CDCl₃)

		Chemical shifts of amide Me protons ^a		$\Delta \delta_{max}$,			<i>T</i> _C ,	ΔG^* .
No.	R	δ_1	δ_2	$(\delta_2 - \delta_1)$	δ_{2-W}	δ_{3*} CH ₃	°Ċ	kcal/mol
1		2.85	2.95	0.1	5.6		22	15.6
2		2.88	2.95	0.07	5.35		- 30	13.1
3		2.88	2.98	0.1	5.42		-25	13.1
4	CH. CH.	3.08	2.38	0.70		1.62	64	16.8
5	CH. CH.CH.	3.06	2.39	0.67		1.65	52	16.2
6	CH. CH. H	3.04	2.40	0.64		1.67	55	16.3

^aFrom TMS as internal standard.

drogen resonance is obtained for the protons belonging to the amide methyls, was determined experimentally in each case. The free energies of activation for the rotation around the C-N amide bond, ΔG^* , were calculated by using the Eyring rate equation^{4,5}

$$\Delta G^* = 4.57 T_{\rm C} [9.97 + \log \left(T_{\rm C} / \Delta \delta_{\rm max} \right)]$$

We have previously employed the intensity ratio method⁶ for the calculation of ΔG^* for some aromatic amides.⁷ This method was not used in the present series as it is known to be unreliable when the coalescence temperatures are lower than 25°.⁸

The temperature dependence of the nuclear resonance has been widely used for the investigation of the rotation about the partial C-N double bond in N,N-dimethylcarboxamides.⁹ The energy requirements for the rotation are dependent upon the nature of the group R. Its electronic effects can influence the nature of the C-N double bond (structure V) and hence the energy requirements for the



rotation. It can also affect the rotation depending upon its size as the steric requirements of the N,N-dimethyl group are quite large. In the present series of N,N-dimethyl-9-carboxamidoacridans, the other substituents in the 9 and 10 position (CH₃ and CH₂C₆H₅) can affect the amide function electronically by their inductive effects alone. As

these are known to be small and the groups are too far removed from the amide function, they cannot influence the electronic contents of these functions to any appreciable extent. Hence, any changes in the rotational barriers must be related to the steric effects of the groups in the 9 and 10 positions.

As a class, the 9-acridan amides bearing a 9-methyl group (a methyl α to the carbonyl) exhibit considerably higher ΔG^* than their counterparts bearing a 9-hydrogen irrespective of the 10 substituent (Table I). This observation is of special significance as in another series of amides α methyls are known to lower ΔG^* . For example, in amides RCON(CH₃)₂ where R is varied from -CH₃, -CH₂-CH₃, $-CH(CH_3)_2$, and $-C(CH_3)_3$, ΔG^* decreases from 18.2 to 12.2 kcal/mol.¹⁰ Thus, in the present series of 9acridan amides the higher ΔG^* must result not from the interactions between the 9-methyl and the amide methyl groups but from increased steric repulsions between the latter and other atoms belonging to the acridan moiety. The atoms most likely to do so are the hydrogens in 1 and 8 positions of the acridan ring system $(H_1 \text{ and } H_8)$. The methyl group in the 9 position is then responsible for altering the conformation of the acridan moiety to cause an *increase* in these interactions. Closer examination of ΔG^* values in Table I shows that in the absence of the 9-methyl group, a 10-methyl or a 10-benzyl causes lowering in ΔG^* (compare 2 and 3 with 1). A 10 substituent, under these conditions, alters the conformation in the opposite direction to cause a decrease in the interactions between the amide methyls and H_1 and H_8 .

Although the unsubstituted acridan (R = H) inverts rapidly between equivalent conformers VI and VII, the presence of a bulky group can bias the equilibrium to favor the conformer where this group occupies a pseudoaxial position (VI).^{11,12} In the parent compound of the present series (1), conformer VI [R = $-CON(CH_3)_2$] is undoubtedly highly favored due to the large bulk of R. Mea-



surements made on a Dreiding model of VII show that the average distance separating the methyl hydrogens and H_1 (or H_8) may be as small as 1.8 Å, considerably shorter than the sum of the van der Waals radii for 2 hydrogens (2.4 Å).¹³ The repulsions between the methyl hydrogens and H_1 , H_8 are at a minimum in conformer VI when the central ring is in a highly puckered boat form with the dihedral angle between the phenyl rings close to 146°.14 These repulsions increase when this angle approaches 180° (when the tricyclic system approaches a planar conformation) and are reflected in the higher ΔG^* for the rotation around C-N amide bond. Our data regarding ΔG^* indicate that the replacement of a 9-H by a methyl group in N,N-dimethyl-9-carboxamidoacridan causes the conformation of the ring system to approach a planar form. In absence of the 9-methyl, a bulky group in the 10 position (such as a methyl or benzyl) has an opposite effect resulting in an decrease in the dihedral angle between the phenyl rings. With two bulky substituents in the 9 position (methyl and N,N-dimethylcarboxamido groups), the large group in the 10 position (methyl or benzyl) has little or no effect, the planar conformation being preferred. Thus, the steric requirements of two large groups in the 9 position seem to take precedence over the needs of the 10 substituent and a flattened time-average conformation is energetically most favorable under these conditions of interaction between two bulky groups in the 9 position and H_1 , H_8 .

The conformational distinction between the 9-monoand 9-disubstituted acridan derivatives is also reflected in the chemical shift differences $(\Delta \delta_{max})$ observed for the amide methyls in these two classes of compounds. The former exhibit "normal" valuest (ca. 0.1 ppm) while in the case of the latter group the values are much higher (0.6-0.7 ppm). An examination of the chemical shifts of the individual methyls reveals that the large difference in the chemical shifts of δ_1 and δ_2 arises mainly due to the large upfield shift in one of the signals (δ_2) . The chemical shift of the other methyl shows a relatively small downfield shift. A reasonable explanation for the upfield shift must lie in the anisotropic shielding effect caused by the ring currents of the π -electron cloud belonging to one of the aromatic rings. Models show that the distance between the aromatic rings and the amide methyls decreases as the conformation of the tricyclic system approaches a planar form. We have shown earlier that when the tricyclic system is completely planar, *i.e.*, in the case of 9-anthracene- and 9-acridine-N, N-dimethylcarboxamides, one of the methyls is highly shielded as seen by the upfield shift (0.35 ppm) of its resonance.⁷ Thus, the upfield shift in δ_2 for the 9-acridan amides bearing a 9-methyl group is

†An examination of data in ref 6, 8, and 15 indicates that for the amides derived from aliphatic carboxylic acids the values for $\Delta \delta_{max}$ lie within the range 0.05-0.13 ppm.



Figure 1.

also consistent with the earlier conclusion that these acridans possess a planar ring system. A large group in the 10 position has little effect on δ_1 and δ_2 , again indicating that the conformation is little affected by a 10 substituent with two bulky groups in the 9 position.

The observation that one of the methyls is highly shielded and the other is somewhat deshielded allows one to determine the positions of these methyl protons with respect to the acridan ring system in a semiquantitative manner. From the Dreiding models and Johnson-Bovey plot of isoshielding lines about a benzene ring,¹⁶ the average position of a proton exhibiting an upfield shift of 0.5 ppm[‡] (amide no. 4, $\sigma_+ = 0.5$) may be calculated as being 3.2 and 2.2 Å (values for Z and ρ , respectively, Figure 1) from the center of the benzene ring.¹⁷ As the protons of the other methyl group are deshielded by 0.2 ppm, their average position must lie close to the line representing σ_{-} = 0.2 on the Johnson-Bovey plot. With one methyl fixed in the position above, the measurements on the Dreiding model indicate that the average position for these protons is represented by 1.75 and 3.8 Å as the values for Z and ρ , respectively (Figure 1). With the position of the C-N bond thus fixed, it is apparent that the rotation around this bond is restricted as during the rotation the distance separating the methyl groups and H_1 (or H_8) is considerably shorter than 3.2 Å, the sum of the van der Waals radii for a methyl group and a hydrogen atom.¹³

The final piece of evidence in support of the conclusion that the conformation is controlled by two bulky groups in the 9 position comes from the chemical shifts of the 9methyl group in the amides 4, 5, and 6. These lie within a narrow range (0.05 ppm) indicating that the chemical environment of the 9-methyl is not affected by the bulk of the group in the 10 position. The chemical shifts of the 9-hydrogen in amides 1, 2, and 3, on the other hand, show much wider variations (0.4 ppm) in support of the conclusion that the bulk of the 10 substituent affects the conformation when only one large group is present in the 9 position.

In conclusion, our results show that the following changes take place in the acridan conformation of N,Ndimethyl-9-carboxamidoacridans upon the introduction of a methyl group in the central ring. (1) A 9-methyl group causes the conformation to approach a planar form. (2) With a methyl group in the 9 position, introduction of another methyl (or benzyl) group in the 10 position does little to alter this flattened conformation of the tricyclic system. (3) With hydrogen in the 9 position, however, an introduction of a methyl (or benzyl) group in the 10 position causes the conformation of the central ring to approach a highly puckered boat conformation.

Although the geometry and electronic structures of the N,N-dimethylcarboxamido side chain and the aminoalkyl side chain $[-(CH_2)_3N(CH_3)_2]$ present in the pharmacologically active derivatives of acridan are different, it is the steric requirement of that portion of the side chain closest

 $[\]ddagger$ The average chemical shift for the amide methyls may be considered to be 2.9 ppm, in the absence of the anisotropic effects of the aromatic rings. The same value (2.9 \pm 0.05 ppm) is consistently exhibited by numerous other amide studies by other workers.

to the acridan nucleus (-CO- and -CH₂-) which is of paramount importance in determining its effect on the conformation. In this respect the steric requirements of the aminoalkyl side chain (with a sp³ hybridized carbon closest to the acridan nucleus) are at least as great as those of the carboxamido (with a sp² hydridized carbon closest to the acridan nucleus) side chain. Hence, we believe that its effects on the acridan conformation must parallel those of the amide side chain in the present study. Thus, it seems that the acridans exhibiting chlorpromazine-like neuroleptic potency (acridans with one large group in the 9 position) are conformationally distinct from those exhibiting imipramine-like antidepressant activity (acridans with two large groups in the 9 position). Although we cannot assert that conformation definitely determines biological activity in the series studied, our work indicates that the observed change in activity is consistent with the conformational changes in the acridan ring system.

Scheme I



Synthetic Methods. The synthesis of N.N-dimethyl-9carboxamido-9,10-dimethylacridan (4) has been reported earlier.¹⁸ All the other amides in Table I were prepared N, N-dimethyl-9-carboxamidoacridine from (7)according to Scheme I. One of the key steps leading to the desired acridans is the reduction of the corresponding acridines and its quarternary salts without affecting the groups in the 9 and 10 positions. Sodium dithionide (hydrosulfite) has been used rather widely as a reducing agent for this purpose.¹⁹ Although this reagent was useful in reducing 7 to 1, during the reduction of 8 the loss of the 10-methyl group was predominant, resulting in the formation of 1 as the major product rather than the desired acridan 2. Both these reductions were carried out in excellent yields by the use of hydrogen over Raney nickel in ethanol at low pressure. However, this reagent was ineffective in obtaining 3 from 9 due to debenzylation during the reduction, 1 being the major product. More surprising was the inability of Raney nickel in ethanol to remove the N-benzyl group from 5 under the same conditions even after 72 hr. The desired reaction (preparation of 6 from 5) was finally performed after the addition of 48% hydrobromic acid to the solvent (ethanol) and the use of palladium

on carbon as the catalyst. Under these conditions about 50% removal of the N-benzyl group was observed after 10 hr. The action of an alkylmagnesium halide on acridine and its quarternary salts is another method of choice in the synthesis of 9,10-disubstituted acridans.²⁰ We have found that this method is not applicable when the acridines possess a carboxamido group in the 9 position. Thus the reactions of 7 and 9 with methylmagnesium iodide did not proceed to any appreciable extent even after the addition of a large excess of the Grignard reagent. Early attempts to methylate 3 to produce 5 by the treatment with a base followed by methyl iodide were unsuccessful due to the tendency of the anion generated from 3 toward aromatization by rapid loss of the N-benzyl group. Thus 7 was the major product when sodium ethoxide and tert-butoxide were employed as bases to produce the anion. This transformation was finally achieved by the use of *n*-butyllithium as the base at low temperatures (below -30°) followed by the addition of methyl iodide. The observation that the benzyl group was unaffected during the reaction is remarkable as we had earlier observed the migration of the N-benzyl group to the 9 position upon the treatment of 9-methyl-10-benzylacridan with n-butyllithium.¹⁸

Experimental Section

Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Ir, nmr, and mass spectra were consistent with structures assigned. Where analyses are indicated only by symbols of the elements, analytical results obtained were within 0.4% of the theoretical value.

Nmr Instrumentations. All the proton magnetic resonance spectra were obtained on a Varian HA-60 spectrometer operating at 60 MHz and a magnetic field strength of 14,096 G. For each compound studied, a 0.5 M solution in chloroform was degassed and sealed under vacuum in a precision-drawn thin-walled nmr tube. The low- and high-temperature spectra were recorded over a series of temperatures on the spectrometer equipped with a V-4343 variable temperature controller. The homogeneity was optimized at each temperature and the spectrum was recorded at a sweeptime of 500 sec and sweep width 50 Hz. Sample temperatures were determined by measuring the potential of a copperconstantan thermocouple junction placed at the bottom of the nmr tube positioned at the standard depth in the probe. A Leeds-Northrup millivolt potentiometer was used to measure the junction potential and was calibrated to 0° by a water-ice bath. Longterm sample temperature control was estimated to be $\pm 0.2^{\circ}$.

N, N-Dimethyl-9-carboxamidoacridine (7). A solution of acridine-9-carboxylic acid (4.5 g, 20 mmol) in 30 ml of thionyl chloride containing a drop of dimethylformamide was refluxed for 2 hr. After removal of thionyl chloride by distillation at low pressure, the brown residue was washed with cold benzene. It was dissolved in 50 ml of dichloromethane and the solution cooled to 0°. Dimethylamine (anhydrous, 3 ml) was added dropwise and the stirring was continued for 12 hr. After filtration to remove dimethylamine hydrochloride, the solution was evaporated to dryness. The solid was dissolved in chloroform and the solution was extracted with 10% potassium hydroxide solution to remove any unreacted acid. The amide was obtained after the removal of chloroform (3.0 g, 60%) and was purified by recrystallization from methanol: mp 170-172°. Anal. (C₁₆H₁₄N₂O) C, H, N.

N.N-Dimethyl-9-carboxamidoacridan (1). A solution of the acridine amide (7, 0.5 g) in 25 ml of 95% ethanol was hydrogenated after addition of catalytic amount of Raney nickel at 40 psi for 6 hr. After removal of the catalyst by filtration and evaporation of the ethanol, the acridan was obtained as a colorless solid: 0.45 g (90%); mp 216-218°. Anal. (C₁₆H₁₆N₂O) C, H, N.

10-Methyl-N,N-dimethyl-9-carboxamidoacridinium Methosulfate (8). To a refluxing solution of N,N-dimethyl-9-carboxamidoacridine (2.5 g, 10 mmol) in 10 ml of toluene, dimethyl sulfate (1.5 g, 12 mmol) was added over 10 min. The mixture was refluxed for 1.5 hr. After cooling to room temperature, the addition of ether (10 ml) resulted in the precipitation of the product as a greenish yellow solid (3.6 g, 95%). It can be obtained in the form of pale green needles after recrystallization from methanol: mp 235° dec. Anal. (C₁₈H₂₀N₂O₄S) C, H, N, S. 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° , nbutyl 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 10benzyl-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. (C₁₇H₁₈N₂O) 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. (C₁₇H₁₈N₂O) 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 (CF₂BrCF₂Br; 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 CCl₃F (fluorocarbon or freon 11) and CF₂BrCF₂Br 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 CF₂BrCF₂Br; when we used a solvent containing CCl₃F and methylcyclohexane but no CF₂BrCF₂Br 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 amides⁵ instead of the decrease of the intensity of the associated band we observed a slower increase in