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Reactivities of Stable Rotamers. XIX. Basicities of Rotameric 9-[2-(Dialkylaminomethyl)-6-methylphenyl]fluorenes and Solvent Effects on Them[1,2]

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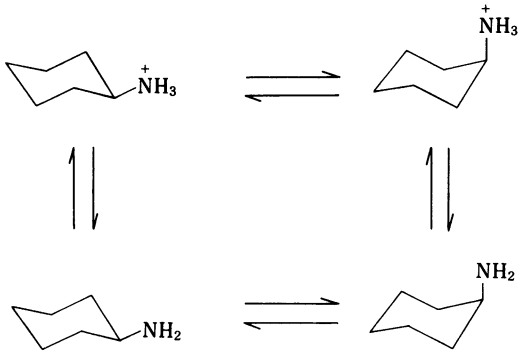
The pK_a' values of the trifluoroacetate salts of the title compounds were determined in THF-water (3:2) solution at 25 °C by potentiometric titration: in every compound examined, basicity of the *ap* rotamer was higher than that of the *sp* rotamer. Differences in pK_a' values (ΔpK_a) between the rotamers are in the range of 0.55 to 1.14 pK_a units, depending upon the substituents on the nitrogen atom. The ΔpK_a values in chloroform-*d* solution at 80.1 °C determined by taking advantage of the equilibrium constants of the salts and the free amines were larger than those obtained in aqueous THF solutions and were nearly independent of the substituents. The results were explained in terms of the intramolecular NH-π interactions in the *ap* salts, which are not possible in the *sp*. ^{1}H and ^{13}C NMR spectral data were in conformity with the presence of the interactions. Examination of the population ratios in various solvents revealed that *sp* conformers of the free amines are generally favored over the *ap* in polar, proton-accepting solvents, but the reverse is true for the trifluoroacetate salts. As the results, ΔpK_a values are large in toluene and chloroform but are rather small in tetrahydrofuran, acetonitrile, and nitromethane. Possible causes for the differences including solvation and hydrogen bond formation are discussed.

Physical properties of an organic compound are often the weighted means of those of several conformers of the molecule, since the interconversion among conformers usually takes place very rapidly. Acidities and basiciteis of organic compounds are examples of those cases. Taking cyclohexylamine, we notice that four processes are involved, as shown in Scheme 1, in the dissociation of this conjugate acid.



Scheme 1. Equilibria involved in dissociation of the conjugate acid of cyclohexylamine.

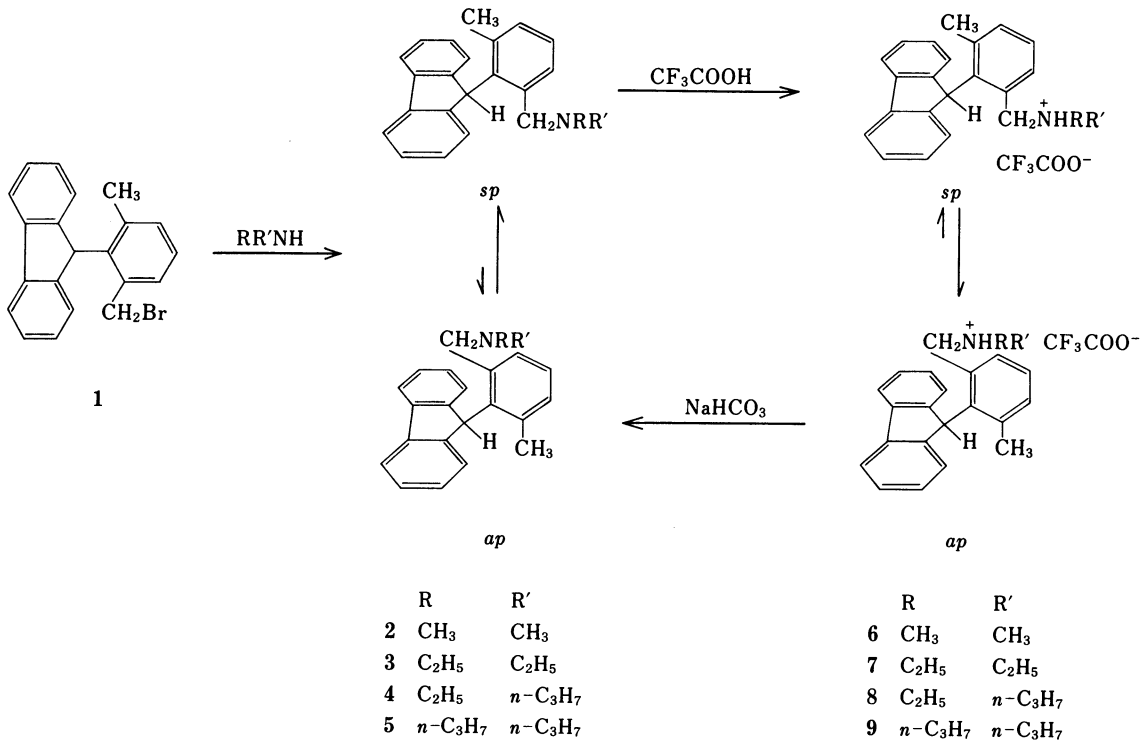
A common method of access to the true pK_a values of the equatorial and the axial conformers of the compound is that we use a pair of model compounds in which inversion and consequently the conformational change in the amine moiety is practically prohibited:[3] 4-*t*-Butylcyclohexylamine is a typical example, the cis isomer modelling the axial isomer and the trans the equatorial isomer.[4] Equations to obtain pK_a values of equatorial and axial isomers of the cyclohexane derivative were derived and were used in determining the pK_a values of axial and equatorial cyclohexylamines from those of cis and trans 4-*t*-butylcyclohexylamines.[4] However, such models possess inherent limitations. If we could directly determine acidities and basicities of respective rotamers, the values would be more reliable than those derived from the models.

Since we were able to isolate rotational isomers at room temperature,[5,6] we have been interested in the reactivities of those isomers.[7] The acidity or basicity is one of the examples in which we can see the respective properties of rotational isomers. The understanding of the acid-base properties of rotational isomers should contribute to get further insight into the bulk properties of organic compounds. Thus we launched a project of determining the acid-base properties of rotational isomers. This paper firstly presents some of the results obtained with 9-[2-(dialkylaminomethyl)-6-methylphenyl]fluorene rotamers both in aqueous THF and in chloroform-*d* and discusses the origin for the difference in basicities of the rotameric amines. The second point presented in this paper is the solvent effects on the base properties which can partly be interpreted on the molecular basis.

Syntheses of Amines

General procedure for the syntheses of the rotational isomers of the amines are shown in Scheme 2. The *sp* rotamer or a mixture of *sp* and *ap* rotamers of 9-(2-bromomethyl-6-methylphenyl)fluorene (**1**) was treated with the excess of the corresponding amines in THF solutions to give *sp*-[2-(dialkylaminomethyl)-6-methylphenyl]fluorenes (**2**—**5**) as a sole product after recrystallization. This stereospecific formation of the *sp* rotamer is interesting. There are two possible reasons for this phenomenon.

The first is kinetic control. Deprotonation reactions of 9-(2-methoxy-1-naphthyl)fluorene[8] and 9-(2-methoxymethyl-6-methylphenyl)fluorene and its analogs[9] with butyllithium followed by protonation with water have been known to produce the corresponding *sp* forms only. This phenomenon is attributed to the structure of the intermediate lithio com-



	R	R′
2	CH_3	CH_3
3	C_2H_5	C_2H_5
4	C_2H_5	n-C_3H_7
5	n-C_3H_7	n-C_3H_7

	R	R′
6	CH_3	CH_3
7	C_2H_5	C_2H_5
8	C_2H_5	n-C_3H_7
9	n-C_3H_7	n-C_3H_7

Scheme 2. Routes of syntheses of amines (**2**—**5**) and their trifluoroacetates (**6**—**9**).

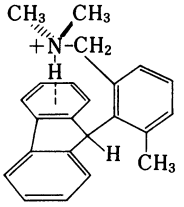
pound which is stabilized by ligation with the heteroatom in the 2-position of the naphthalene or the phenyl nucleus, and protonation of the lithio compound with retention of configuration.[10] However, it is difficult to find this type of factors for the selectivity of the reaction.

The second is the thermodynamic effect which may favor the *sp* forms. Isomerization of the 9-arylfluorene rotamers takes place when an amine is present:[11] Under the reaction conditions the *sp* and *ap* amines can isomerize and thermal equilibrium may be reached. When we treated a mixture of *sp* and *ap* rotamers of compound **1** (*sp* : *ap*=1 : 2.7) with excess of dimethylamine in a THF solution and quenched with dilute hydrochloric acid after 30 min, we found that *sp* and *ap* amines were obtained in a 6.1 : 1 ratio. This ratio increased to 10 : 1 if the reaction period was lengthened. We conclude from this together with the similar results obtained for the diethylamine and dipropylamine cases that the overwhelming formation of the *sp*-amines is due to thermodynamic control. The equilibrium data obtained here are a little different from those in THF, as discussed later, but the results can be attributed to the presence of excess of amines which are polar and favor the solvation of the *sp* forms.

According to the above results, we have to use another independent way of synthesis to prepare the *ap*-amines. We found, however, that the *ap*-amine trifluoroacetate salts were much more stable than the *sp* in chloroform. Thus heating a chloroform solution of the *sp*-salt at 80.1 °C for 7 d afforded a mixture of rotational isomers, in which the ratio *ap*/*sp* reached nearly 10 or more. The pure *ap* salts were then obtained by recrystallization of the mixture from ether. Treatment of the salts with aqueous sodium hydrogencarbonate produced pure *ap*-amines. The predominance of the *ap* form over the *sp* in chloroform must be derived by the presence of NH-π interactions in the *ap* form, which will be discussed below in more detail.

9-[2-(Dimethylaminomethyl)-6-methylphenyl]fluorene

At the outset of the project, we measured the pK_a' values of rotameric 9-[2-(dimethylaminomethyl)-6-methylphenyl]fluorene trifluoroacetate in 3 : 2 THF-water. The pK_a' values were 5.85 and 6.45 for the *sp* and *ap* forms, respectively. The results were rather unusual in the sense that the amine moiety which is located in a more crowded site is more basic than that in a less crowded site: The general tendency, that is, less crowded amines are more basic than crowded amines, is explained on the basis of the unfavorable solvation of the crowded ammonium moiety.[4,12] There can be various reasons for the anomaly but we wished to focus our attention to the possible presence of the NH-π interactions (**10**), which are possible for



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the *ap* salt but impossible for the *sp* due to the unfavorable approach of the NH group to the π-system of the fluorene, as the main cause.

Although the OH-π interactions are well documented,[13] the NH-π interactions are rarely reported.[14-16] From the available data, however, the presence of the NH-π interactions is clearly favored when the NH groups becomes electronegative, as is expected from the charge transfer theory. Since the electronegativity of the $^{+}$NH group is very high, it will be reasonable to assume the presence of the NH-π interactions here.

If the NH-π interactions play an important role in stabilizing the *ap* form of the salt relative to the *sp*, then the relative stability should be enhanced in less electron-donating solvents in hydrogen-bond formation, since the competition of the intramolecular NH-π interactions with the hydrogen-bond formation with such solvents will become favorable for the former. Being one of those solvents, chloroform is expected to show a large difference in pK_a values of the rotational isomers of **6**. However, it is very difficult to measure pK_a values in chloroform in the usual sense.

If one is allowed to discuss the difference only, not the absolute values, then there is a trick. The K_a values of the respective rotamers can be expressed by Eqs. 1 and 2.

$$K_a(sp) = \frac{[sp\text{-amine}][CF_3COOH]}{[sp\text{-salt}]} \quad (1)$$

$$K_a(ap) = \frac{[ap\text{-amine}][CF_3COOH]}{[ap\text{-salt}]} \quad (2)$$

Dividing Eq. 1 by Eq. 2, we obtain

$$\frac{K_a(sp)}{K_a(ap)} = \frac{K(\text{salt})}{K(\text{amine})} \quad (3)$$

where K(salt) and K(amine) are equilibrium constants (*ap*/*sp*) of the salt and the free amine, respectively, in chloroform at a given temperature. Then the ΔpK_a values ($\Delta pK_a = pK_a(ap) - pK_a(sp)$) can be obtained by taking the logarithm of Eq. 3, because K(salt) and K(amine) are measurable quantities.

Before getting into discussion of the ratios of the dissociation constants in chloroform, there is one thing which we should not overlook. Due to poor solvation in chloroform, dissociation of trifluoroacetic acid in this solvent should be greatly depressed,[17] or the ammonium salt **6** should be unstable. There is a chance that **6** dissociates into the free amine **2** and trifluoroacetic acid in chloroform to some extent. In order to find out if this is the case, we observed the chemical shifts of the NMR signals due to the benzylic methylene protons and 9-H by gradually adding trifluoroacetic acid to a solution of *sp*-**2** in chloroform-*d*. The results are shown in Fig. 1. As is clear from the Figure, the methylene proton signal at δ 3.69 for the free amine moved to a lower magnetic field on addition of the acid until it reached, on addition of 1.0 equivalent of the acid, at δ 4.63, where it stayed on further addition of the acid. The 9-H signal showed the similar behavior though it moved to a higher magnetic field on protonation of the amine. These clearly indicate that the ammonium salt *sp*-**6** exists without appreciable dissociation into the free amine and the acid under the conditions.

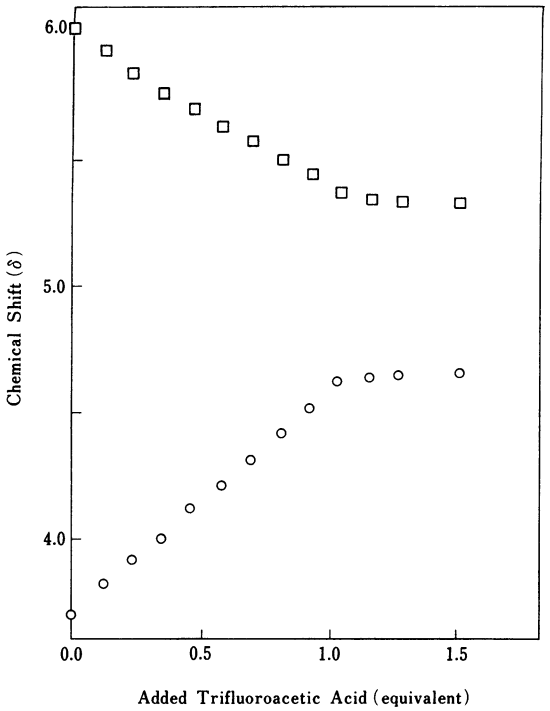

Fig. 1. Dependence of chemical shifts of benzylic protons and 9-H of *sp*-9-[2-(dimethylaminomethyl)-6-methylphenyl]fluorene in $CDCl_3$ on the amount of added trifluoroacetic acid.

In chloroform-*d*, the population ratio (*ap*/*sp*) of the rotamers of the free amine **2** was found to be 1/3.66, whereas that of the ammonium salt **6** was 9.70. Thus the ΔpK_a value in $CDCl_3$ is calculated to be 1.55. This enhancement of the difference in pK_a values of the rotamers in chloroform relative to the value in THF-water supports the idea of the presence of the NH-π interactions in the *ap* form of the salt.

9-[2-(Dialkylaminomethyl)-6-methylphenyl]fluorenes

Since the solvation effects are found to be very important in determining the pK_a values, we have extended the work to see the effects of the alkyl chain length in 9-[2-(dialkylaminomethyl)-6-methylphenyl]fluorenes (**2—5**) and their salts **6—9**. Since the alkyl chain should affect the solvation energy, there should be a chance that enhanced difference in pK_a values is observed. They may as well provide additional evidence for the presence of the NH-π interactions in the *ap* forms, when we compare the data in the series of compounds.

^{1}H and ^{13}C NMR Spectra. The ^{1}H NMR spectral data are given in Table 1. The free amines show fea-

Table 1. ^{1}H NMR Chemical Shift Data (δ) of Amines **2**—**5** and Their Trifluoroacetate Salts **6**—**9** in $CDCl_3$

Compound	Form	CH(α)[a]	CH(β)[a]	CH(γ)[a]	Aromatic CH_3	Benzylic CH_2	9-H
2	*sp*	2.32	—	—	1.10	3.69	6.02
	ap	1.51	—	—	2.70	2.11	5.44
3	*sp*	2.59	0.98	—	1.00	3.83	6.14
	ap	1.86	0.48	—	2.70	2.19	5.50
4	*sp*	2.6 2.5	0.97 1.43	— 0.73	1.10	3.86	6.17
	ap	1.83 1.70	0.57 0.90	— 0.46	2.70	2.17	5.43
5	*sp*	2.43	1.43	0.77	1.09	3.83	6.11
	ap	1.67	0.85	0.53	2.63	2.13	5.48
6	*sp*	2.97	—	—	1.17	4.63	5.33
	ap	1.93	—	—	2.76	2.98	5.53
7	*sp*	3.30	1.40	—	1.16	4.63	5.34
	ap	2.13 2.47	0.66	—	2.75	2.94	5.53
8	*sp*	3.37 3.1	1.40 1.83	— 1.00	1.17	4.70	5.30
	ap	b)	0.6 1.0	— 0.6	2.73	2.9 3.1	5.50
9	*sp*	3.20	1.81	1.00	1.17	4.70	5.29
	ap	1.97 2.24	1.00	0.63	2.73	2.97	5.57

a) α, β, and γ denote the position from the N atom in the alkyl chain. b) Multiplets centering at δ 1.7 (1 H) and 2.3 (3 H) that are not assigned.

tures that are common for the 9-arylfluorene series: The aromatic methyl and benzylic methylene signals are placed at high fields when the groups are located over the fluorene ring. Even the protons involved in the alkyl groups show similar tendency, though the effect becomes smaller as the protons are located remote from the nitrogen atom.

The change in the chemical shifts on protonation is very large especially for the protons of the methylene (methyl) groups which are attached directly to nitrogen. Inspection of the data in detail reveals that the extent of the low field shifts is different in *sp* series from that in the *ap* for some protons. Whereas the benzylic methylene signals of both *sp* and *ap* amines are similarly shifted to a low field by 0.8—0.9 ppm when the amines are protonated, the proton signals ascribable to the methylene (hereafter *N*-methylene) or the methyl group which is directly bonded to the nitrogen are shifted differently in the *sp* form from those in the *ap*. In every compound examined, the change in chemical shifts of the *N*-substituent protons is smaller in the *ap* form than in the *sp* on protonation. The dipropylamino compound **5** and its conjugate acid **9** are typical examples. The difference in the chemical shifts of the *N*-methylene proton signals is 0.77 ppm on protonation of the *sp* rotamer, while that of the *ap* rotamer is 0.44 ppm. These results may be explained on the basis of the freedom of motion of the propyl group. On one hand, the location of the benzylic methylene group is more or less fixed because of the rigidity of the part of the molecule. On the other, the *N*-methylene group can take various positions due to the conformational change in the free amine, while the position is rather fixed in the salt because of the presence of the NH-π interactions. Thus in the *ap* salt, the *N*-methylene protons are placed in the shielding region of the fluorene nucleus to counterbalance the effect of protonation to some extent and to make the smaller shifts to the low field on protonation. A similar tendency is observed in the 2-methylene protons and the methyl protons in the propyl group, though the extent of the difference becomes smaller as the protons become more remote from the nitrogen, the phenomenon being again in conformity with the freedom of motion of the propyl group.

The ammonium NH protons, though not listed in Table 1, show signals at δ ca. 11.5 and 12.5 for the *ap* and the *sp* conformers, respectively. The placement of the NH protons of the *ap* form at a higher magnetic field than that of the *sp* is another support for the presence of the NH-π interactions: The ring current effect of the fluorene ring should bring the chemical

Table 2. ^{13}C NMR Chemical Shift Data (ppm from TMS) of Amines **2**—**5** and Their Trifluoroacetate Salts **6**—**9** in $CDCl_3$

Compound	Form	N-C(α)[a]	N-C(β)[a]	N-CH(γ)[a]	Aromatic CH_3	Benzylic CH_2	9-C
2	*sp*	45.46	—	—	18.54	64.72	49.70
	ap	45.07	—	—	22.05	59.50	49.80
3	*sp*	46.04	11.23	—	18.54	58.57	49.41
	ap	46.38	11.13	—	21.91	53.16	49.80
4	*sp*	46.48	11.08	—	18.59	59.11	49.41
		55.01	19.66	12.01			
	ap	47.16	11.03	—	21.96	53.60	49.80
		54.92	19.66	11.91			
5	*sp*	55.55	19.52	12.06	18.69	59.60	49.41
	ap	55.79	19.71	11.91	21.96	54.14	49.80
6	*sp*	42.48	—	—	19.23	58.09	49.74
	ap	41.95	—	—	22.05	56.48	49.21
7	*sp*	45.94	8.79	—	19.23	53.36	49.70
	ap	45.12	7.57	—	22.05	52.39	49.27
8	*sp*	47.02	8.69	—	19.23	54.14	49.70
		53.06	17.13	11.13			
	ap	46.73	7.28	—	22.05	53.20	49.26
		51.89	16.15	10.93			
9	*sp*	53.45	17.03	11.18	19.23	54.18	49.70
	ap	52.58	15.72	10.99	22.01	53.26	49.21

a) α, β, and γ denote the position from the N atom in the alkyl chain.

shift of the NH protons in the *ap* forms to a high field.

It deserves mention here that the *N*-methylene protons of the *ap* forms of **7** and **9** exhibit AB pattern signals, if we neglect couplings with methylene or methyl protons, at room temperature to indicate that they are diastereotopic. It is also characteristic that the benzylic methylene protons in the *ap* forms give doublet signals. These should mean that the proton attached to the nitrogen atom dissociates slowly on the NMR time scale. Since the *N*-methylene protons of the *sp* forms do not show the diastereotopic nature nor the benzylic protons doublet signals at this temperature, the dissociation of the NH proton must be taking place much faster in the *sp* than in the *ap* form. The slow dissociation of the ammonium proton in the *ap* forms offers additional evidence for the presence of the intramolecular NH-π interactions. The details of the dynamic behavior will be described elsewhere.

The ^{13}C NMR spectral data shown in Table 2 indicate that the difference in chemical shifts between *sp* and *ap* rotamers are in most cases very small, less than 1.5 ppm. The exceptions are the benzylic methylene and aromatic methyl carbons of which differences amounted to 3.5—5.5 ppm in free amines. Although the presence of the ring current effect in ^{13}C NMR spectra is controversial,[18] it is tempting to consider that the ring current effect is operative in this case because of the proximity concerned. The most striking feature of the ^{13}C NMR spectra is the change in chemical shifts of the benzylic methylene carbons when the amine is protonated. In the case of *sp* amines, these carbons moved toward a high magnetic field by at least 5 ppm, while shifts were less than 0.8 ppm except for one case, a pair of **2** and **6**, in the *ap* forms. Since the protonation of amines usually causes a 3—5 ppm high field shift of the carbon signals alpha to the amino group,[19] the change in chemical shifts observed in the *sp* series is normal but that for the *ap* series abnormal. The contrast must be attributed to some effects of the substituents peculiar to the *ap* series.

We wish to attribute again the difference to the conformational change in the salt from that in the free amine. The repulsive interactions between lone-pair electrons and the aromatic π-system seem to be great. For example, the *sp* rotamer of 9-(2-methoxy-1-naphthyl)fluorene predominates over the *ap* form, although the half thickness of a benzo group is larger than the van der Waals radius of the oxygen atom in a methoxyl group.[20] Thus the conformation in which the amino-nitrogen is located closely to the fluorene ring is strongly disfavored. The preferred conformation must be such that the amino moiety takes a position away from the fluorene ring. This will necessarily result in the placement of the benzylic methylene protons, where they face the fluorene ring. This will cause the van der Waals shift for both hydrogens and

Table 3. Equilibrium Constants (*ap*/*sp*) of Amines **2**—**5** and Their Salts **6**—**9** in $CDCl_3$ at 80.1 °C, Ratios of Dissociation Constants, and Differences in pK_a Values

R[a)]	R'[a)]	K_{amine}	K_{salt}	K_{ap}/K_{sp}	ΔpK_a
CH_3	CH_3	1/3.7	9.7	36	1.5_5
C_2H_5	C_2H_5	1/2.8	12	34	1.5_3
C_2H_5	*n*-C_3H_7	1/2.5	14	35	1.5_4
n-C_3H_7	*n*-C_3H_7	1/2.2	22	48	1.6_8

a) R and R' in Scheme 2.

Table 4. Rate Constants of the Internal Rotation about the C_9–C_1' Bond in the Amines **2**—**5** and the Salts **6**—**9** in $CDCl_3$ and Free Energies of Activations at 80.1 °C

Compound	Process *sp*→*ap*		Process *ap*→*sp*	
	k	$\Delta G^{\neq}$[a)]	*k*	$\Delta G^{\neq}$[a)]
	$10^{-6}\ s^{-1}$	kcal mol^{-1}	$10^{-6}\ s^{-1}$	kcal mol^{-1}
2	0.85	30.59	3.12	29.68
3	0.61	30.83	1.71	30.10
4	0.69	30.72	1.71	30.10
5	0.48	31.00	1.06	30.44
6	4.73	29.39	0.49	30.99
7	12.6_5	28.70	1.03	30.46
8	9.42	28.80	0.67	30.77
9	7.22	29.10	0.33	31.26

a) 1 cal=4.184 J.

carbons,[21] by which carbon signals are shifted to a high field. In *ap* salts, the conformation is such that the NH-π interactions are possible in it: This requires that at least one of the methylene protons is placed away from the fluorene ring.

Rotational Barriers and Rotamer Populations. Mere consideration of the rotamer populations in equilibrium in discussing the stability of rotamers can lead to an erroneous conclusion, because one rotamer can be rich in population for two reasons; its enhanced stability relative to others and the enhanced instability of the counterparts. In order to diagnose the two possibilities, determination of rotational barriers should lend help, if the transition state for rotation can be assumed nearly equal. Thus we determined the rotational barriers and equilibrium constants in chloroform-*d* at 80.1 °C. The results are shown in Tables 3 and 4.

As is seen in Table 3, the equilibrium constants show a remarkable contrast for every compound examined: In amines, the *sp* forms are favorable species, being consistent with the general tendency that a bulkier substituent takes a position close to the 9-H in 9-(2,6-disubstituted phenyl)fluorenes,[6] while in the salts *ap* forms predominate by a factor of 10—20. The results are in conformity with the presence of the NH-π interactions in the *ap* forms of the salt.

As to the kinetics of internal rotation in amines, the rates of rotation as well as the free energy of activation for rotation are by and large the same irrespective of the alkyl chain, although a slight enhancement of the barrier is observed when one goes from methyl to ethyl and then to propyl (Table 4). This will mean that we may assume that both the ground states and the transition states for rotation are almost the same in their energy in these amines, as far as the molecular interactions are concerned. On protonation of the amine, the transition state energy of rotation will be slightly enhanced, if not the same with the amine, but the degree of the enhancement will be very small. Kinetic data in Table 4 then show that the ground state of the *sp* salt is destabilized to a small extent: This will probably because of the unfavorable steric effects on solvation. In contrast, the barrier to rotation for the process *ap*→*sp* is clearly enhanced in the salt relative to the free amine. If one takes the unfavorable solvation effects seen in the *sp* form of the salt and that the situation is even enhanced in the *ap* salt into consideration, the natural conclusion is that the *ap* form of the salt is stabilized relative to the *sp* forms due to the presence of the NH-π interactions in the former.

Difference in pK_a Values. The ΔpK_a values in chloroform-*d* are given in the last column of Table 3. Generally the difference is invariant. However, if one takes a careful look at the individual data, one notices that both *K*(amine) and *K*(salt) change as the alkyl group changes: Both the *K*(amine) and *K*(salt) values increase as the alkyl chain is lengthened. As a result, the ΔpK_a values appear to be not affected by the chain length. However, the population ratios of the salt change significantly when the alkyl chain becomes long. This is probably because the solvation becomes inefficient for the *sp* forms of the salt as the alkyl chain is lengthened, while the NH-π interactions are still

Table 5. pK_a' Values and Concentrations of the Conjugate Acids **6—9** in 3:2 THF-Water at 25°

Compound	pK_a'	*sp* Concentration / mol L^{-1}	pK_a'	*ap* Concentration / mol L^{-1}	ΔpK_a
6	5.90	0.0071	6.45	0.0059	0.55
7	5.70	0.0059	6.80	0.0072	1.10
8	5.22	0.0059	6.15	0.0059	0.93
9	4.98	0.0059	6.12	0.0077	1.14

efficient in the *ap* salt. In the free amine, the solvation effect is as well important: The solvation energy becomes small as the alkyl chain is lengthened, thus making the unfavorable steric situation for the *ap*-amine less effective.

The pK_a' values of the conjugate acids **6—9** were measured in 3:2 tetrahydrofuran-water. The results are given in Table 5. It is interesting to note that the ΔpK_a value of the methyl compound **6** is now doubled when we go to the ethyl compound **7**, whereas the ΔpK_a values do not change on further lengthening of the alkyl chain. The pK_a' values of the *sp* conjugate acids decrease monotonously when one goes from the short alkyl chains to long alkyl chains, while those of the *ap* forms show a maximum at the ethyl compound. Literature search reveals that the series of *N,N*-dialkylanilines shows the maximum basicity at the ethyl compound,[22] and the diethyl compound is more basic than the dimethyl compound in the series of *N,N*-dialkylbenzylamines,[22] though the exact cause for this phenomenon is not yet identified. It is possible that the monotonous decrease in the pK_a' values in the *sp* series is due to the steric hindrance for solvation, whereas in the *ap* the trend is normal because of the presence of the NH-π interactions. The stable conformation of the dimethylammonio group in the *sp* form of **6** will be such that the dimethylammonio group is perpendicular to the benzene ring of the 2,6-disubstituted phenyl group, as is the case of neopentylbenzene derivatives.[23] In this conformation, a water molecule can approach the ammonio-proton to form a hydrogen bond without much steric hindrance from the direction which is perpendicular to the phenyl ring. By contrast, the conformation of the diethylammonio group in the *sp* form of **7** will be such that the diethylammonio group takes a position in which the group opposes the 3-H of the phenyl ring. This is caused by severe steric interactions of the methyl group in the diethylammonio with the hydrogens at 1 and 8 positions of the fluorene ring. This conformation is unfavorable for solvation due to the steric effect, because the most stable conformation in this frame will be such that the hydrogen on the nitrogen atom of the ammonio group is located closely to the 3-H of the phenyl ring.

The sudden jump in the ΔpK_a value of the diethyl compound from the dimethyl may be ascribed to the NH-π interactions again. Due to the intramolecular interactions, the unfavorable steric effects on solvation are somewhat erased in the *ap* form relative to that of the *sp* form to make the *ap* amine more basic than the *sp*. The same factor operates in compounds with long alkyl chains (**8** and **9**) but the effect of solvation energy must be leveled off to make the apparent ΔpK_a almost the same.

Table 6. Equilibrium Constants (*ap*/*sp*) of Amines **2—5** and Their Salts **6—9** in Various Solvents at 80.1°C

Compound	Toluene-d_8	THF	CH_3CN	CH_3NO_2
2	1/5.2	1/6.8	1/6.8	1/6.5
3	1/4.5	1/6.5	1/6.4	1/6.1
4	1/4.3	1/5.3	1/5.0	1/5.0
5	1/4.1	1/4.0	/3.9	1/4.0
6	4.1	1.0	1.0	2.2
7	7.4	2.1	1.9	2.5
8	7.9	2.1	3.0	3.4
9	11	2.3	3.4	3.4

Solvent Effects

The discussion presented above emphasizes that the NH-π interactions are important in affecting the difference in basicities of the rotamers in question. Chloroform is a solvent which does not donate electrons in hydrogen bond formation,[24] while the THF-water system may be taken as that NH-O hydrogen bond formation is possible between the solute and the solvent. Thus in THF-water a competition exists between the NH-O hydrogen bond and the NH-π, the former being more favored in terms of enthalpy at least than the latter. Thus it becomes of interest to examine the generality of the effect of hydrogen bond formation on the basicity difference of the rotamers. In this connection, we have examined the pK_a differences in various solvents.

The selected solvents are toluene, tetrahydrofuran, acetonitrile, and nitromethane. Toluene was assumed to be only weakly active in hydrogen bond formation and nonpolar, whereas latter three are capable of hydrogen bonding and polar. The results of the equilibrium constants and $\Delta pK_a'$ s are shown in Tables 6 and 7, respectively.

Table 7. Differences in pK_a Values (ΔpK_a) in Various Solvents at 80.1 °C

R[a)]	R'[a)]	Toluene-d_8	THF	CH_3CN	CH_3NO_2
CH_3	CH_3	1.33	0.83	0.83	1.16
C_2H_5	C_2H_5	1.52	1.14	1.08	1.18
C_2H_5	n-C_3H_7	1.53	1.05	1.18	1.23
n-C_3H_7	n-C_3H_7	1.65	0.96	1.12	1.13

a) R and R' in Scheme 2.

As to the populations of free amines, every solvent used here favors the *sp* forms relative to chloroform. As far as the polar solvents are concerned, the results may be attributed to the favorable steric situation of the *sp* forms for solvation. The population ratios in chloroform and toluene are not explainable in a straightforward manner but they may well be due to the solvation effect again: While toluene is a large molecule which should suffer from the steric effects in solvating the *ap* form, the largest solvation effect by the chloroform molecule should be given by hydrogen-bond formation, where chloroform acts as proton donor[25] and steric requirement is rather small. Close examination of Table 6 reveals that in every solvent examined, the *ap*/*sp* ratios decrease as the chain length of the alkyl group becomes longer. The long alkyl chain seems to disfavor the stabilization due to solvation of the *sp*-amines relative to the *ap*-amines, because intrinsic steric hindrance is larger in the latter than in the former even in the short chain case: The solvation energy becomes relatively less in the *sp* form as the alkyl chain becomes long. Although dielectric constant does not seem to play any role in the population ratio in the proton-accepting solvents, the reason for this phenomenon is not well-understood at the present.

By contrast, the *ap* forms of the amine salts are favored over the *sp* forms except for **5** in THF and acetonitrile, for which the equilibrium constants are 1.0, still a larger value than any of the amines examined. It is reasonable that the equilibrium constants are rather small in polar, hydrogen-bond accepting solvents. Because of the competition between the solute-solvent hydrogen bond and the intramolecular NH-π hydrogen-bond, the former being favored in terms of enthalpy, at least some fractions of the solute molecules will take conformations which are favorable for the intermolecular hydrogen bond but disfavor the intramolecular one. Since the entropic effect is not favorable for the intermolecular hydrogen bond, the intramolecular NH-π bond may still be present in the *ap* form in proton-accepting solvents. It is possible that this effect is partially responsible to the favorable population of the *ap* form relative to the *sp*. The slight increase in the *ap*/*sp* values of every compound in THF, acetonitrile, and nitromethane as the chain is lengthened may be explained similarly as above by the steric effect on solvation.

Toluene gives interesting but puzzling results. If the polarity of the solvent were important in determining the equlibrium constants, this solvent should have given larger *ap*/*sp* values for the salts than chloroform. Since the *ap*/*sp* values of the salts were all smaller in toluene than in chloroform, there must be other factors to be considered. First is the fact that toluene is a π-base. There must be a competition between intramolecular and intermolecular NH-π hydrogen bonds. Even though the entropy effect is not favorable for the intermolecular hydrogen bond, the solute-solvent interaction, such interactions should exist at least to some extent. Second is the fact that chloroform is capable of forming a hydrogen bond. This ability will contribute to stabilizing the *ap* salts by forming a hydrogen bond with the carboxylate anion in addition to the NH-π bond relative to the *sp* salts which exist as tight ion pairs, forming a hydrogen bond between the ammonium ion and the carboxylate anion.

As the results of these factors including the NH-π interaction and the solvation of the free amines and the salts, the differences in pK_a values must be derived (Table 7). It is interesting that in proton accepting solvents the ΔpK_a values are very close to 1.0 pK_a unit, whereas the solvents which cannot form a strong hydrogen bond with the NH group give large differences. The largest ΔpK_a value was obtained for the dipropylamino-compound in $CDCl_3$ with the close second of the same compound in toluene. The results suggest that in nonpolar aprotic solvents, the ΔpK_a values of rotational isomers can be great under certain conditions.

In summary, the results described here clearly demonstrate that the acidity or basicity is different from one rotamer to another and that the solvent effect on the difference is important. The causes for the differences can be the steric effects on solvation and intramolecular interactions such as the NH-π. Although it has not been explicitly discussed in this paper, the steric hindrance to proton abstraction may be a factor to be considered. It is necessary to interpret the pK_a value of a compound by taking the following factors into consideration in addition to the solvation or the intermolecular interactions: The populations and basicities of rotamers concerned which may be affected by intramolecular interactions.

Experimental

Syntheses of Amines 2—5 and Their Trifluoroacetates

Table 8. Melting Points, Yields, and Analytical Data of Amines and Their Trifluoroacetates

Compound	Form	Mp θ_m/°C	Yield/%	Analyses C(%) Found	C(%) Calcd	H(%) Found	H(%) Calcd	N(%) Found	N(%) Calcd
2	*sp*	87—88[a]	82[b]						
	ap	90—91[a]							
3	*sp*	67—68	68	87.79	87.93	7.75	7.97	3.96	4.16
	ap	38—40	85	87.74		7.77		3.94	
4	*sp*	36—38	73	88.10	87.84	7.97	8.22	3.79	3.94
	ap	Oil	76	87.58		8.05		3.86	
5	*sp*	96—97	68	87.58	87.75	8.26	8.46	3.64	3.79
	ap	22—26	84	87.51		8.55		3.65	
6	*sp*[c]	168—170	82	69.11	70.25	5.40	5.66	3.19	3.28
	ap[c]	162—165	71	69.43		5.77		3.44	
7	*sp*	155—157	79	71.17	71.19	6.23	6.20	2.93	3.08
	ap	143—145	70	71.19		6.22		2.89	
8	*sp*[c]	118—120	82	70.70	71.62	6.28	6.44	2.93	2.98
	ap	93—95	76	71.34		6.46		2.78	
9	*sp*	139—142	83	71.94	72.03	6.66	6.67	2.62	2.90
	ap	138—140	72	71.94		6.66		2.72	

a) These compounds had been prepared in alternative ways.[9] b) The yield of the amine prepared by the method described in this paper. c) These compounds seem to contain 0.04—0.09 equivalent excess of trifluoroacetic acid, of which presence was confirmed by ^{19}F NMR spectra. The trifluoroacetic acid could not be removed by heating at 80°C in vacuo for several hours.

6—9. General procedures for the syntheses are described by taking the diethyl compound **3** and **7** as examples. The melting points, yields, and analytical data are given in Table 8.

***sp*-9-[2-(Diethylaminomethyl)-6-methylphenyl]fluorene (*sp*-3).** To a solution of 245 mg (0.70 mmol) of a rotameric mixture of 9-(2-bromomethyl-6-methylphenyl)fluorene (**1**)[26] (*sp*/*ap*=2) in 20 mL of tetrahydrofuran, was added 2.0 g (27.3 mmol) of diethylamine. The solution was stirred at 40 °C for 24 h and then the reaction mixture was poured into 30 mL of water. The mixture was extracted with ether and the ether extracts were dried over sodium sulfate. After evaporation of the solvent, the residue, of which ^1H NMR spectrum showed to be a 10:1 mixture of *sp* and *ap* amines, was submitted to silica-gel TLC. Elution with dichloromethane-ethanol (10:1) afforded 163 mg (68%) of *sp*-**3**. Recrystallization from methanol afforded pure samples.

sp-**3** trifluoroacetate (*sp*-**7**) was prepared by adding 1 mL of trifluoroacetic acid to a solution of 80 mg of *sp*-**3** in 10 mL of ether followed by stirring for 10 min. Evaporation of the solvent together with excess of trifluoroacetic acid in vacuo and then two successive recrystallizations of the residue from ether afforded a pure sample.

ap-**3** trifluoroacetate (*ap*-**7**) was obtained by heating a solution of 30 mg of *sp*-**7** in 0.5 mL of chloroform-*d* in a sealed tube at 80.1 °C by immersing the tube in a boiling benzene bath for 7 d. The ratio *ap*/*sp* of the trifluoroacetate was 12 at this stage. The product was recrystallized from ether to give pure *ap*-**7**.

ap-**3** was obtained by treating a solution of *ap*-**7** in dichloromethane with 3% aqueous sodium hydrogencarbonate. The product was purified by recrystallization from methanol.

Preparation of the dimethylamino compound **2** has been reported[9] but *ap*-**2** was more conveniently prepared by the analogous procedure described above. The results are also included in Table 8.

Some of the *ap* amines had low melting points. In these cases, the free amines were purified by chromatography on silica gel, thoroughly dried in vacuo and submitted to elemental analyses.

pK_a' Measurements. In a typical experiment, 66.9 mg of *sp*-**7** was dissolved in a 25 mL volumetric flask in 3:2 THF-water to make a 0.0059 mol L^{-1} solution. By the use of a pipet, 10 mL of this solution was placed in a two-necked flask and was titrated with a 0.083 mol L^{-1} sodium hydroxide solution in 3:2 THF-water. Evaporation of THF was prevented as much as possible by using small inlets for the buret and for a glass electrode. After a small portion of the sodium hydroxide was added, the pH value of the solution was read by the glass electrode. In one experiment, 20 to 30 points were obtained. The curve which shows the relationship between the added sodium hydroxide and the pH values is simulated by the use of a computer program[27] to get a best fit. The pK_a' values are tabulated in Table 5.

NMR Measurements. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer operating at 89.55 and 22.49 MHz for proton and carbon, respectively. Some of the ^{13}C signals were assigned on the basis of off-resonance experiments and comparison of the peak intensities of the spectra obtained by the gated decoupling mode.

Kinetic Measurements. The rates of isomerization were

determined by monitoring the increase or decrease of the ^{1}H NMR signals due to each isomer in chloroform-*d* solutions. Plots of $\ln[1-(1+1/K)(a/X)]$ vs. time gave a straight line and the first order rate constants were obtained by the conventional method. In some salts in $CDCl_3$, the equilibrium constants seemed too large to afford reliable values by the NMR method. In such cases, the equilibrium constants were determined by treating them as variables starting from the NMR values: They were obtained as values which gave the best straight line in the plots of $\ln[1-(1+1/K)(a/X)]$ vs. time. Agreement between the calculated values and the observed ones by the NMR method was fairly good.

Determination of the Equilibrium Constants in Various Solvents. The amine or the salt was dissolved in a pure solvent under nitrogen and the solution was sealed in a tube, which was immersed in a boiling benzene bath (80.1 °C). It took 7 d to reach equilibrium at that temperature. The sealed tube was opened and the solvent was evaporated in vacuo. The population ratio, *ap/sp*, was determined by the integrated intensities in the ^{1}H NMR signals of the product in $CDCl_3$. In the case of salts, a small quantity of trifluoroacetic acid (0.05—0.10 equivalent) was added to avoid the presence of a free amine which would affect the equilibrium constant to a great extent. The effect of the presence of trifluoroacetic acid on the equilibrium was negligible, because changing the quantity of the acid within the range mentioned above did not show any significant difference in the equilibrium constants.

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