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BASICITY OF ROTAMERIC 9-(2-DIMETHYLAMINOMETHYL-6-METHYLPHENYL)FLUORENE[1)]

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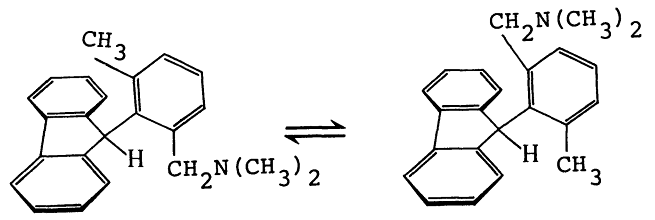
The pKa' values of the conjugate acids of the title compound were determined as 5.85 and 6.45, respectively, for the sp and ap isomers by potentiometric titration in THF-water solutions. The difference was ascribed to the existence of N-H···π interactions in the ap rotamer on the basis of the equilibrium constants between and barriers to rotation in rotamers of the conjugate acids and the free bases.

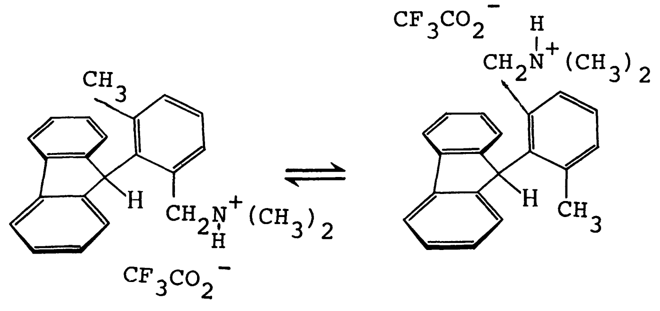
Physical properties of an organic compound are often the average of those of several conformers of the molecule, since the interconversion among conformers usually takes place very rapidly. Acidities and basicities are one of such cases. For example, the pKa of cyclohexanecarboxylic acid is the average of the pKa's of axial and equatorial carboxyl groups. One of the ways to estimate the properties of individual rotamers was to measure such properties of model compounds: although one can not obtain the intrinsic pKa values for each conformer of cyclohexanecarboxylic acid due to the fast ring inversion, one can assume that they are similar to those of cis- and trans-4-t-butylcyclohexanecarboxylic acid, respectively, because a bulky t-butyl group always takes an equatorial position.[2)] However, the model systems are limited and the inherent assumption that the model produces good approximation can cause argument.

Since we were able to isolate rotational isomers at room temperature,[3-5)] it is now possible to measure pKa values of rotamers without any assumption. In this paper, results of a study on the difference in pKa' values observed in the conjugate acids of rotameric 9-(2-dimethylaminomethyl-6-methylphenyl)fluorene, sp-1 and ap-1, will be reported together with the discussion on the reasons for the difference.

Amines, sp-1 and ap-1, were prepared by the reaction of dimethylamine with sp and ap forms of 9-(2-bromomethyl-6-methylphenyl)fluorene,[6)] respectively. Addition of excess of aqueous trifluoroacetic acid into an ether solution of the amine gave the corresponding salts, sp-2 and ap-2, which were then recrystallized from ether.



sp-1 ap-1



sp-2 ap-2

For the determination of pKa' values, a THF-water (3:2) solution of each rotamer of the salts(2) was prepared (concentrations between 6 x 10^{-3} and 2 x 10^{-2} mol L^{-1}) and potentiometric titration was carried out by the addition of sodium hydroxide in a mixed solvent of the same composition. Computer simulation of the observed curve yielded the pKa' values of the sp- and ap-salt as 5.85 and 6.45, respectively.

These values are unusually small compared with that of a similar tertiary ammonium salt such as N,N-dimethylbenzylammonium salt (pKa = 9.02).$^{7)}$ Solvent polarity is one of the reasons for this.$^{8)}$ In fact, pyridinium trifluoroacetate showed a pKa value of 5.25 in water while the value was 4.20 in THF-water (3:2) solutions. But the major contribution to the small pKa' values seems to be an unfavorable solvation toward the cationic center of the protonated species due to steric hindrance.

As for the difference in pKa's between the rotamers, the sp-salt turned out to be a stronger acid than the ap-salt by 0.6 pKa unit. This is unusual in a sense that the dimethylamino group of the ap-amine which is supposed to be in a sterically more crowded site has a stronger ability to accept proton than that of the sp-amine: a base in sterically hindered site is usually weaker than a corresponding base in less hindered site because of the solvation effects.$^{8)}$ The results indicate that the difference in free energies between the system of the amine plus the acid and that of the salt is smaller in sp forms than in ap forms.

In order to obtain more information on the reasons for the difference in pKa' values, we measured the equilibrium constants and free energy of activation for rotation of the amines and the salts by monitoring the increase and decrease in the intensity of N,N-dimethyl signals in ^1H NMR spectra at 80.2 °C in chloroform-d and the results are listed in the Table 1.

Table 1. Equilibrium Constants and Kinetic Data for sp-ap Systems of 1 and 2 at 80.2 °C in $CDCl_3$

	K(ap/sp)	$k_{sp \rightarrow ap}$	$k_{ap \rightarrow sp}$	$\Delta G^{\ddagger}_{sp \rightarrow ap}$	$\Delta G^{\ddagger}_{ap \rightarrow sp}$
		10^{-6} s^{-1}	10^{-6} s^{-1}	kcal mol^{-1}	kcal mol^{-1}
1	1/3.4	0.75	2.54	29.6	28.8
2	9.7	4.99	0.51	28.3	29.9

Surprisingly, the equilibrium constant in the salt showed a remarkable contrast to that in the free amine. In the amine, the sp form was a favorable species which is consistent with the general tendency that a bulkier substituent takes a position close to the 9-H in 9-(2,6-disubstituted phenyl)fluorenes.[5)] In the salt, on the contrary, the ap form predominates by a factor of 9.7. As for the free energy of activation for rotation, $\Delta G^{\ddagger}$, examined for the process from sp to ap, it decreased by 1.3 kcal mol^{-1} on going from the amine to the salt, while that for the process from ap to sp increased by 1.1 kcal mol^{-1} on going from the free amine to the salt. Since the energy level of the transition state for rotation of the salt is expected to be higher than that of the amine due to the increased bulkiness of the nitrogen substituent, the results of the free energies of activation demonstrate that the sterically more hindered ap form was stabilized to a large extent relative to the less crowded sp form by protonation. The unusual result can be explained if we consider the existence of an intramolecular N-H$\cdots\pi$ interaction between the ammonium N-H group and the fluorene π-system in the ap-salt.

From the equilibrium constants listed in the Table we can calculate the ratio of acid dissociation constants, $K_a(sp\text{-}\underline{2})/K_a(ap\text{-}\underline{2})$, in $CDCl_3$ by the equation given below:

$$K_a(sp\text{-}\underline{2})/K_a(ap\text{-}\underline{2}) = K(salt)/K(amine)$$

Since K(amine) and K(salt) are 1/3.4 and 9.7, respectively, the ratio is calculated to be 33 which indicates that the sp salt is stronger as an acid than the ap salt by 1.5 pKa units. Thus the difference is enhanced when one goes from aqueous THF to chloroform. The result is consistent with the presence of the N-H$\cdots\pi$

interaction, since it is expected to become a major attractive force in a nonpolar aprotic solvent, whereas other stabilization such as N-H···O hydrogen bond is possible in an aqueous THF solution.

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