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Solvent Effects in NMR Spectroscopy. I. Chemical Shifts Induced by the Addition of Protic Substances to Benzene Solutions of Several Polar Compounds

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The variations in the chemical shifts of proton resonances in some polar compounds in benzene solution, when a portion of protic substances, methanol or trifluoroacetic acid, is added, are determined. It is found that protons of a solute molecule undergo an upfield shift which is enhanced by an increase in the concentration of added protic substances. The protons lynig in proximity to the proton-accepting center of the molecule are more sensitive to this upfield shift than are those far remote from it. The shifts induced by the addition of protic substances to a benzene solution are shown to be applicable to the structural determination; this proves to be useful in obtaining informations about the hydrogen bonding.

Studies of the specific interaction between a polar solute and an aromatic solvent are now well established.[1] It has been shown that benzene-solvent molecules can form a stereospecific complex with ketone, amide, and some other polar functional groups in a solute molecule in a manner which permits us to derive valuable stereochemical and structural conclusions from the solvent shift data.[1] Although the nature of this specific interaction has not been made clear, the approximate orientation of the complexing benzene molecule has been proposed with respect to the carbonyl group in the cases of amides,[2] unsaturated ketones,[1] alicyclic ketones,[3] and some other carbonyl compounds.

We found that the addition of a portion of protic substances, methanol or trifluoroacetic acid, for example, to a benzene solution of, for instance, acetone, methyl isopropyl ketone, or *N*, *N*-dimethylformamide, causes an upfield shift of the protons of the solute molecules. This is also the case for other polar molecules, ether, amine, ester, and so on, but not for nonpolar compounds, cyclohexane, and *n*-pentane, for example, which are inert to the hydrogen bonding.

It seemed of interest to investigate this phenomenon systematically in order to elucidate its intrinsic origin and also to apply it to the structural determination, in hopes of obtaining further evidence of the specific interaction between benzene and polar molecules.

In this paper, we will discuss the chemical shifts induced by the addition of the protic substances to benzene solutions of several polar compounds, *i. e.*, (a) *N*, *N*-disubstituted amides and nitrosamines, (b) α, β-unsaturated carbonyl compounds, (c) alicyclic ketones, and (d) azabenzenes. Also, the tentative generalization will be proposed that the protons lying in the vicinity of the proton-accepting center undergo much more of a upfield shift than those located far from it.

Experimental

All of the compounds studied in the present work were obtained from commercial sources and were purified carefully before use. The proton magnetic resonance spectra were obtained at 60 Mc/sec with a JEOL JNM-3H-60 NMR spectrometer, modified as will be described below. This spectrometer has two types of NMR control systems, an external locking system (the so-called two-sample NMR control) and an internally-locked field-frequency control (the one-sample NMR control). In the present work the spectra were obtained using the latter control system for the precise field-frequency stabilization, using the tetramethylsilane (TMS) internal reference signal and the field sweep method. The sweep speed was of the order of 0.1 cps/sec, and the chemical shifts were measured in cps with a digital frequency counter from an internal TMS. The accuracy of the measurements is within 0.1 cps for the chemical shift.

Solutions for the PMR spectra were prepared in such a way that the concentrations were approximately 5% v/v in both benzene and carbon tetrachloride solutions unless otherwise noted. To these solutions, protic substances, trifluoroacetic acid or methanol, were added drop by drop, the total volume being estimated in advance.

1) a) N. S. Bhacca and D. H. Wiliams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif. (1964), Chap. 7. b) See T. Ledaal, *Tetrahedron Letters*, **1966**, 1653, and the references therein.

2) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **5**, 139, 153 (1962).

3) J. D. Connolly and R. McCrindle, *Chem. Ind.*, **27**, 379 (1965).

Results and Discussion

(a) Amides and Nitrosamines. The chemical shifts[4] induced by the addition of methanol or trifluoroacetic acid to a 5% v/v benzene solution of *N*, *N*-disubstituted amides and nitrosamines are listed in Table 1, together with the shifts[5] on passing from a carbon tetrachloride to a benzene solution ($\Delta\nu_{CCl_4}^{C_6H_6}=\nu_{CCl_4}-\nu_{C_6H_6}$). This addition shift is given by:

$$\Delta\nu_{C_6H_6}^{TFA} = (\nu_{C_6H_6} - \nu_{C_6H_6+TFA}) - (\nu_{CCl_4} - \nu_{CCl_4+TFA})$$

It corresponds to the difference in the chemical shift between the chemical shift induced by the addition of the protic substances to the benzene solution and that for the carbon tetrachloride solution. This correction is adopted in order to avoid any effect of the protonation or hydrogen bonding on the chemical shift of the solute molecule.[6] This method of correction will also be adopted for other compounds belonging to other groups.

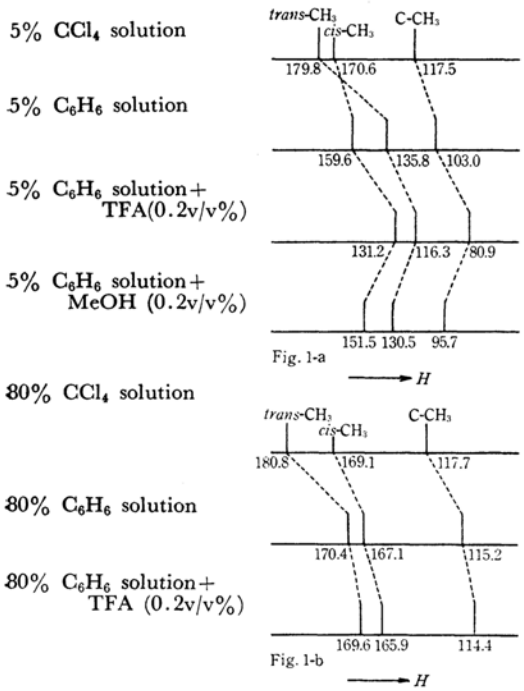


Fig. 1. Schematic illustrations of the effect of additive protic substances on the methyl proton shifts for benzene solution of *N*, *N*-dimethylacetamide (5% solution Fig. 1-a; 80% solution Fig. 1-b). The figures are chemical shifts in cps from TMS.

Table 1 and Fig. 1 illustrate that, in general, the methyl or methylene protons *cis* to the carbonyl group for amides are more remarkably subject to the addition of the protic substances than are the *trans* protons. This upfield addition shift is just the opposite of the benzene solvent shift and is more conspicuous for TFA than for methanol. In *N*, *N*-dimethylacetamide, for example, the *cis* methyl group exhibits a much larger upfield shift than does the *trans* or the C-methyl group. The order of these unequal upfield shifts is just the opposite of that observed on going from the CCl_4 to the benzene solution. In fact, the addition shift, $\Delta\nu_{C_6H_6}^{TFA}$, is of the order: *cis*-CH_3>C-CH_3>*trans*-CH_3, whereas the benzene solvent shift, $\Delta\nu_{CCl_4}^{C_6H_6}$, increases in an order such as: *trans*-CH_3>C-CH_3 *cis*-CH_3.

As is shown in Fig. 1, the order of the addition shift for *cis*-CH_3 and *trans*-CH_3 protons is not dependent on the concentration of amide in the benzene solution. In the dilute benzene solution (Fig. 1-a), the *trans N*-methyl protons resonate at a higher field than do the *cis*, contrary to the behavior of the CCl_4 solution with the corresponding concentration, while the chemical shift difference between the *cis* and *trans* methyl protons decreases when protic substances are added to this benzene solution. On the other hand, contrary behavior is seen in a more concentrated solution (Fig. 1-b). It should also be noted that, for the dilute benzene solution, the magnitude of the addition shift is in the order of *cis*-CH_3>*trans*-CH_3>C-CH_3 at low concentrations of the additive TFA, while at appropriate concentrations an order such as *cis*-CH_3>C-CH_3>*trans*-CH_3 is observed, as may be seen in Fig. 2, where the value of $\Delta\nu_{C_6H_6}^{TFA}$ is plotted against the concentration of the added TFA. The change in the order of $\Delta\nu_{C_6H_6}^{TFA}$ for *trans*-CH_3 and C-CH_3 groups may arise from the change in the polarity of the amide molecule. The small amount of TFA added might serve to increase the polarity of the amide molecule, thus facilitating the formation of a collision complex between a benzene and an amide molecule. On the other hand, at higher concentrations of TFA, specific interaction between benzene and additive TFA might occur in the vicinity of the carbonyl oxygen atom, leading to a more appreciable upfield shift for the C-CH_3 protons than for the *trans*-CH_3 protons.

As is indicated in Table 1, for nitrosamines, unlike *N*, *N*-disubstituted amides, the difference in

4) This shift will henceforth be referred to simply as the addition shift, $\Delta\nu_{C_6H_6}^{TFA}$, where TFA denotes trifluoroacetic acid.

5) This shift will also be designated as the benzene solvent shift, $\Delta\nu_{CCl_4}^{C_6H_6}$.

6) T. Yonezawa, I. Morishima and M. Fujii, to be published.

TABLE 1. CHEMICAL SHIFTS INDUCED BY THE ADDITION OF PROTIC SUBSTANCES TO THE BENZENE SOLUTION OF AMIDES AND NITROSAMINES

Solute molecule		ν_{CCl_4} [a]	$\nu_{C_6H_6}$ [a]	$\Delta\nu_{CCl_4}^{C_6H_6}$, [b] cps	$\Delta\nu_{C_6H_6}^{TFA}$, [c] cps	$\Delta\nu_{C_6H_6}^{MeOH}$
N, *N*-Dimethylacetamide						
CH_3 *trans*	C-CH_3	117.5	103.0	+14.5	+22.1	+7.6
CH_3 *cis*	*cis*-CH_3	170.6	159.6	+11.0	+28.4	+8.1
	trans-CH_3	179.8	135.8	+44.0	+19.5	+5.3
N, *N*-Dimethylformamide						
H, CH_3 *trans*	*cis*-CH_3	168.4	145.5	+22.9	+23.7	
CH_3 *cis*	*trans*-CH_3	176.8	121.6	+55.2	+17.8	
N, *N*-Diethylformamide						
	cis-CH_3	65.3	51.7	+13.6	+6.1	
H, CH_2CH_3 *trans*	*trans*-CH_3	70.8	39.7	+31.1	+4.7	
CH_2CH_3 *cis*	*cis*-CH_2	200.0	190.0	+10.0	+10.6	
	trans-CH_2	200.6	161.0	+39.6	+6.0	
N, *N*-Dimethylnitrosamine						
CH_3 *trans*	*cis*-CH_3	177.8	144.1	+33.7	+17.8	
CH_3 *cis*	*trans*-CH_3	225.3	178.4	+46.9	+16.5	
N, *N*-Diethylnitrosamine						
	cis-CH_3	62.7	43.2	+19.5	+14.9	
CH_2CH_3 *trans*	*trans*-CH_3	83.4	52.3	+31.1	+12.7	
CH_2CH_3 *cis*	*cis*-CH_2	213.8	193.5	+20.3	+24.0	
	trans-CH_2	250.7	219.7	+31.0	+23.9	

a) Chemical shift in cps from an internal TMS.
b) 5 v/v % for CCl_4 and benzene solution.
c) TFA trifluoroacetic acid (0.2 v/v %).

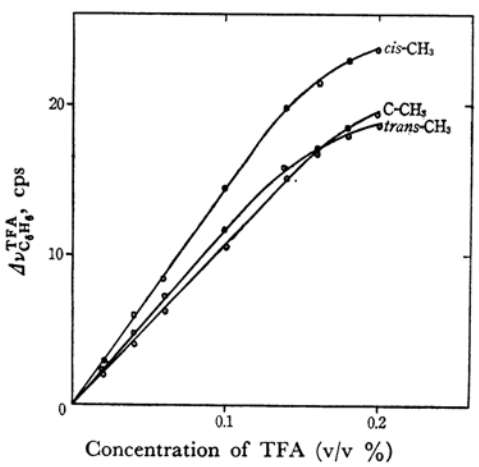


Fig. 2. Plot of $\Delta\nu_{C_6H_6}^{TFA}$ *vs.* the concentration of additive TFA for *N*, *N*-dimethylacetamide.

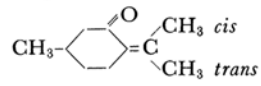
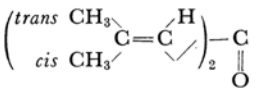
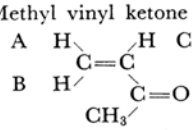
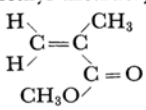
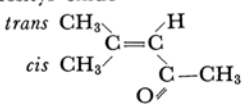
the addition shift for *cis* and *trans* methyl or methylene protons is small, although the value of $\Delta\nu_{C_6H_6}^{TFA}$ is appreciably large. Similar behavior is also observed in oxime.[7] It should be noted that both nitrosamines and oximes have two lone pairs available for the proton acceptor, *i. e.*, the lone pairs of oxygen and nitrogen atoms in both compounds. Providing that the upfield addition shift, $\Delta\nu_{C_6H_6}^{TFA}$, more evident for the proton in the vicinity of the proton acceptor, as has been discussed in connection with *N*, *N*-disubstituted amides, is mainly due to the hydrogen bonding, the anomalous features for nitrosamines and oximes may arise from the hydrogen bonding occurring at two sites to a greater extent at the oxygen atom for nitrosamines.

From the results presented in Table 1, it may be seen that the benzene solvent shift is larger for the proton far from the negative center, and *vice versa* for the addition shift. These facts seem to be governed by a simple factor, the distance between the proton in question and the negative center of the molecule. This proposal will be further verified in the cases of the following groups of polar compounds.

(b) α, β-Unsaturated Carbonyl Compounds. The results for several α, β-unsaturated carbonyl compounds are presented in Table 2. The assignments of the various methyl protons may be confirmed by considering the solvent shifts, $\Delta\nu_{CCl_4}^{C_6H_6}$, for pulegone and phorone. That is, the methyl

7) T. Yonezawa, I. Morishima and K. Takeuchi, unpublished results.

TABLE. 2. CHEMICAL SHIFTS INDUCED BY THE ADDITION OF TFA TO THE BENZENE SOLUTION OF α, β-UNSATURATED CARBONYL COMPOUNDS

Solute molecule		ν_{CCl_4}	$\nu_{C_6H_6}$	$\Delta\nu_{CCl_4}^{C_6H_6}$, cps	$\Delta\nu_{C_6H_6}^{TFA}$, cps	
Pulegone						
	*cis*-CH_3	115.6	122.1	−6.5	+17.5	
	trans-CH_3	105.8	87.8	+18.0	+14.8	
	C-CH_3	63.4	46.0	+17.4	+6.7	
Phorone						
	*cis*-CH_3	128.3	132.1	−3.8	+18.5	
	trans-CH_3	112.7	93.3	+19.4	+9.9	
Methyl vinyl ketone						
	A	—[b]	—[b]	+23.8[b]	+1.1[b]	
	B	—	—	+19.1	+3.6	
	C	—	—	+11.6	+6.2	
Methyl methacrylate						
	C-CH_3	115.0	108.7	+6.3	+0.8[c]	+10.0[d]
	O-CH_3	221.7	202.2	+19.5	+0.2	+13.9
Mesityl oxide						
	*cis*-CH_3	124.6	123.3	+1.3	+15.7	
	trans-CH_3	110.2	86.1	+24.1	+7.7	
	C-CH_3	123.1	109.8	+13.3	+14.5	

a) The concentration of the additive TFA is *ca.* 0.2 % v/v.
b) Only the relative shifts which can be obtained without exact analyses are cited here.
c) The concentration of the additive TFA is *ca.* 0.01 % v/v.
d) The concentration of the additive TFA is *ca.* 0.1 % v/v.

protons undergoing a larger upfield shift are identified as *cis* methyl protons with respect to the carbonyl group, and those with less of an upfield shift, as *trans*. Obiously, in this case also, the addition shift, $\Delta\nu_{CCl_4}^{TFA}$, is larger for protons lying nearer to the carbonyl oxygen atom. For rigid molecules, pulegone and phorone, existing in an *s-cis* form, *cis* methyl protons are barely shifted upfield more noticeably than the remaining methyl protons. For methyl vinyl ketone, which is considered to be present in an *s-trans* form, the *cis* proton (designated as B) undergoes more of an upfield shift than the *trans* proton (A) when TFA is added to a benzene solution. It can be seen that, whereas the order of $\Delta\nu_{CCl_4}^{TFA}$ values for vinyl protons is the same as that of $\Delta\nu_{CCl_4}^{C_6H_6}$ values, unlike the cases for *s-cis*-type compounds (amide, pulegone and phorone), the tendency for the proton situated close to the proton-accepting center to undergo more of an upfield shift is also the case for *s-trans*-type methyl vinyl ketone.

These types of correlations may prove to be very useful in the assignment of methyl resonances for a compound in which a number of unsplit methyl signals are encountered, for example, mesityl oxide. Mesityl oxide, the conformation of which has been in dispute,[8] it being unclear whether an *s-cis* form or an *s-trans* form exists predominantly, is of interest for the present study in that the addition shift is possibly a helpful means for the structural determination. The spectral assignment for the C-methyl signal in either a benzene and carbon tetrachloride solution is simple, but that for *cis* or *trans* methyl groups with respect to the carbonyl bond is ambiguous. Hatton and Richards[2] have proposed an *s-trans* mesityl oxide complexed with benzene as in Fig. 3; they assigned the methyl

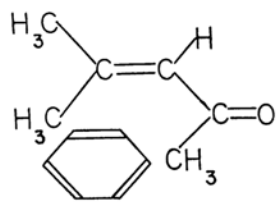


Fig. 3. A structure of the benzene-mesityl oxide complex proposed by Hatton and Richards (Ref. 2).

8) J. E. Baldwin, *J. Org. Chem.*, **30**, 2423 (1965).

signals at a higher field as *cis* methyl protons. However, there has been no direct evidence for the predominant *s-trans* form. Rather, it has been concluded by some workers, using other methods, that an *s-cis* mesityl oxide is most probable.[8]

For mesityl oxide, the addition shift, $\Delta\nu^{TFA}_{C_6H_3}$, is also largest for the protons which are least sensitive to the solvent effect of benzene. Similar behavior has been found in the rigid molecules, pulegone and phorone, existing in the *s-cis* form (see Table 2). If one assumes that mesityl oxide exists in an *s-trans* form, as has been indicated by Hatton and Richards, the addition shift, $\Delta\nu^{TFA}_{C_6H_6}$, will be larger for C-methyl and *cis* methyl protons than those for *trans* methyl protons in the *s-trans* form. In other words, for an *s-trans* form, the $\Delta\nu^{TFA}_{C_6H_3}$ values should increase in the order: $COCH_3 > cis\text{-}CH_3 > trans\text{-}CH_3$. This contradicts the experimental results that the values of $\Delta\nu^{TFA}_{C_6H_6}$ are in the order: $cis\text{-}CH_3 > COCH_3 > trans\text{-}CH_3$, which is just the opposite of the case of the solvent shift, $\Delta\nu^{C_6H_6}_{CCl_4}$, namely: $trans\text{-}CH_3 > COCH_3 > cis\text{-}CH_3$. If one assumes that mesityl oxide exists in an *s-cis* form, the order of the addition shift for methyl protons stated above is rationally acceptable and the similarity in the behavior of $\Delta\nu^{C_6H_6}_{CCl_4}$ and $\Delta\nu^{TFA}_{C_6H_6}$ values for mesityl oxide and of those of pulegone and phorone in an *s-cis* form is self-explaining. Accordingly, an *s-cis* form of mesityl oxide may reasonably be thought to exist, for this is in accordance with the studies of the IR,[9] Raman,[10] dipole moment[11] and NMR values of related compounds.[8]

The most remarkable feature of the addition shift for methyl methacrylate is the crossing of the two plot lines of the $\Delta\nu^{TFA}_{C_6H_6}$ value against the volume of the TFA added to C–CH_3 and –OCH_3 protons. When there is a small amount of TFA, C–CH_3 protons undergo a larger upfield shift than –OCH_3 protons do, while an increase in the amount of TFA added to a benzene solution leads to a reverse observation, as is illustrated in Fig. 4. This behavior is understandable if we formulate benzene collision complexes as occurring nearly at the carbonyl oxygen atom at low concentrations of TFA and at the –OCH_3 oxygen atom with increased amounts of TFA. This observation is consistent with the behavior in nitrosamine and oxime, each with two sites available for the proton acceptor.

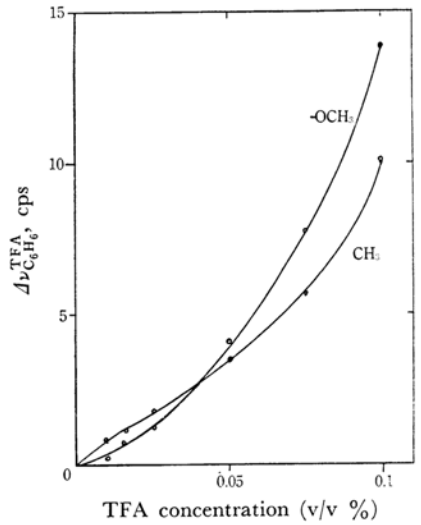


Fig. 4. Plot of $\Delta\nu^{TFA}_{C_6H_6}$ *vs.* the concentration of additive TFA for methyl methacrylate.

(c) Alicyclic Ketones. To evaluate further the order of the magnitude of the addition shift for steroidal ketones with methyl protons which lie in positions at various distances and in various directions from the proton-accepting center, a conformationally-rigid model is needed. Camphor, camphorquinone, and fenchone were chosen for this purpose.

The effect of benzene as a solvent on the methyl proton shift of these alicyclic compounds has been studied by Connolly and McCrindle;[3] their assignment of the methyl resonances is used in our work, along their procedure. The results presented in Table 3 also suggest an empirical correlation which states that the order of the addition shift, $\Delta\nu^{TFA}_{C_6H_6}$, is just the opposite of that of the solvent shift. It is also revealed that the more remote from the carbonyl oxygen atom the methyl group is, the larger is the solvent shift, $\Delta\nu^{C_6H_6}_{CCl_4}$, and the smaller is the addition shift. Of the three related alicyclic compounds in Table 3, 10-methyl protons undergo more of an upfield shift than do 8- or 9-methyl protons, which lie more remote from the carbonyl oxygen; further, the 8-methyl protons shift upfield more markedly than does 9-methyl, in accordance with the tentative correlation between the addition shift and the distance from the negative center to the proton in question. For fenchone, 8- and 9-methyl proton signals split into a doublet on passing from the CCl_4 solution to the benzene solution; neither of these can be assigned. The lower-field signal of the two becomes more shielded than the other upon the addition of TFA to a benzene solution. Also, in these two methyl protons the tendencies of the addition shift and the solvent shift are just the reversed.

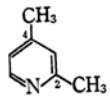
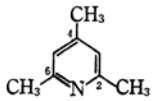
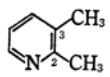
9) R. Mecke and K. Noack, *Chem. Ber.*, **93**, 210 (1960); R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, **1960**, 3425.
10) K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 220 (1961).
11) J. B. Bently, K. B. Everard, R. J. B. Marsden and L. E. Sutton, *J. Chem. Soc.*, **1949**, 2957.

TABLE 3. CHEMICAL SHIFTS INDUCED BY THE ADDITION OF TFA TO THE BENZENE SOLUTION OF ALICYCLIC KETONES

Solute molecule		ν_{CCl_4}	$\nu_{C_6H_6}$	$\Delta\nu^{C_6H_6}_{CCl_4}$, cps	$\Delta\nu^{TFA}_{C_6H_6}$, a) cps
Camphor					
	8-CH_3	49.7	35.2	+14.5	+10.7
	9-CH_3	57.0	38.0	+19.0	+9.4
	10-CH_3	55.5	53.4	+2.1	+14.4
Camphorquinone					
	8-CH_3	55.5	31.0	+24.5	+4.0
	9-CH_3	63.1	26.5	+36.6	+2.4
	10-CH_3	63.9	48.9	+15.0	+7.5
Fenchone					
	10-CH_3	65.5	66.3	+0.8	+12.6
	8,9-CH_3	59.7	{53.2 {55.0	{+6.5 {+4.7	{+11.1 {+12.4

a) The concentration of the additive TFA is *ca.* 0.2 % v/v.

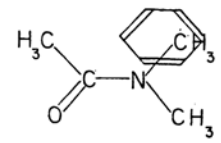
TABLE 4. CHEMICAL SHIFTS INDUCED BY THE ADDITION OF TFA TO THE BENZENE SOLUTION OF AZABENZENES

Solute molecule		ν_{CCl_4}	$\nu_{C_6H_6}$	$\Delta\nu^{C_6H_6}_{CCl_4}$, cps	$\Delta\nu^{TFA}_{C_6H_6}$, a) cps
2,4-Lutidine					
	4-CH_3	135.7	110.7	+25.0	+5.6
	2-CH_3	146.0	145.3	+0.7	+8.4
2,4,6-Collidine					
	4-CH_3	132.0	113.2	+18.8	+5.8
	2-CH_3	142.8	145.3	+2.5	+5.9
2,3-Lutidine					
	3-CH_3	133.8	108.9	+24.9	+6.6
	2-CH_3	145.4	141.2	+4.2	+8.5

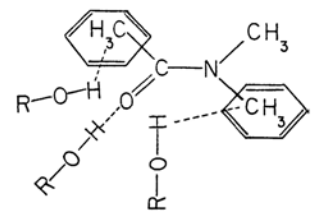
a) The concentration of the addition TFA is *ca.* 0.2 %.

(d) Azabenzenes. Table 4 presents the results for 2, 3-, 2, 4-lutidine, and 2, 4, 6-collidine. The difference in the methyl proton shifts seems to provide further support for our above generalization. These results are also consistent with the formation of the type of collision complex occurring in the vicinity of the nitrogen atom in a benzene solution containing a portion of TFA.

The present results and the discussions for several groups of polar compounds have led to an interpretation of the intrinsic addition shift. Namely, this shift may be due to acid- or alcohol-benzene interaction occurring at the proton-accepting center when a portion of acid or alcohol is added to a benzene solution of polar molecules. The driving force facilitating the approach of benzene molecules to the negative center of the solute molecule seems to arise from the hydrogen bonding of an acid or



a. Benzene solution



b. Benzene solution +Protic substance

Fig. 5. A possible structure of the benzene-amide complex in the absence or presence of a portion of protic substance R-OH.

alcohol added to π electrons of benzene (the well-known intermolecular π-type hydrogen bonding) occurring in the vicinity of the proton-accepting center. This is shown in the model pictured in Fig. 5. However, the validity of this type of interaction is still uncertain. The nature of the weak interaction in a benzene solution containing a small amount of protic substances is open to further investigation; work is now in progress, and the results will be published in the future.

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