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43. Yutaka Kawazoe,[*1] and Masako Ohnishi[*2] : Nuclear Magnetic Resonance Studies. IV.[*3] Solvent Effect of Trifluoroacetic Acid on Proton Resonances.

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Nuclear magnetic resonance spectroscopy has become a powerful tool in the solution of qualitative analytical problems in organic chemistry, as in diverse other fields. One of the many characteristic and superior advantages of this spectroscopy is that the characterization of the protons can be easily made, mainly based on the fact that the chemical shifts shown by various sorts of protons are characteristic for the ones in chemically different locations of the molecule. Thus, the magnitudes of the chemical shifts can give quite useful informations on the chemical structure.

However, it might be more helpful if another method could be found out, besides a consideration of the resonance positions, to support and ascertain the proposed structural assignments, so that the reliability of the assignment would be increased. It is also desirable to find out the method to distinguish protons from each other which resonate at the same field, even if they are placed in the different chemical environments.

Due to the above considerations, our attention has been paid on the fact that any heteroatoms (or any functional groups containing these atoms) might be considered as basic or acidic compared to the carbon atom. Their affinities with acidic or basic reagents must be different from each other, depending on the basicity or the acidity of these atoms or functional groups. As the basicities are increased, for instance, (acetylated alcoholic oxygen, ether oxygen and then, amine nitrogen) acidic reagents must affect these basic centers to bring the more neutralizing effect to the resonance positions of their neighbouring protons. It might be expected that the magnitude of the shift differences between in acidic and neutral solvents must be characteristic for the respective functional group, although the more consideration should be paid for the numerical correlation between the shifts and the basicity.

In this paper, the trifluoroacetic acid was used as an acidic medium and the differences of the chemical shifts observed in this acid from those in carbon tetrachloride were correlated with the solvent effect of this acid in order to see the general features of the neutralizing effect. Since a limited number of the samples were examined for each type of protons, further investigations should be advanced for the more detailed discussion, which are being pursued in our laboratories.

Trifluoroacetic acid has been often used as an effective solvent for nuclear magntic resonance measurements of special types of compounds, e.g., quaternary amine salts, amino acids and peptides. As pointed out by Tiers,[1,2] it is an excellent solvent not only for various organic substances but also for ionic compounds such as ammonium salts, betain, etc. It enables us, therefore, to employ cyclohexane or tetramethyl silane as an internal reference. For the present purpose, this acid can be considered as the most convenient proton-donor medium, since it is a very strong acidic and light liquid and gives no nuclear magnetic resonance signal on the spectrum except for that of

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[*3] Part Ⅲ. T. Okamoto and Y. Kawazoe : This Bulletin (1963), to be published.

1) G. V. D. Tiers : J. Phys. Chem., **62**, 1151 (1958).

2) F. A. Bovey, G. V.D. Tiers : J. Am. Chem. Soc., **81**, 2870 (1959).

acidic proton.[*4] In spite of its superiority mentioned above, one unavoidable disadvantage of this acid was encountered when alcohols and phenols were examined. Namely, since trifluoroacetic acid is an acylation reagent by itself, they are promptly acetylated even at room temperature, usually to give a spectrum of a mixture of the original samples and their trifluoroacetyl derivatives. The acylable substances, therefore, could not help being excluded from this study.

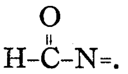
Experimental

Most of the compounds examined were commercially available and some of them were prepared by authentic synthetic methods. NMR spectra of the compounds were obtained both in ca. 5% CCl_4 and ca. 5% F_3CCOOH solutions by a Varian Associates DP-60 NMR spectrometer (60 Mc.p.s.) or a Japan Electron Optics Laboratory Co., Ltd. JNM-3 NMR spectrometer (40 Mc.p.s.). The chemical shifts were given in p.p.m. unit from the signal of the internal cyclohexane. With regard to the sign of the shift differences reported in this paper, the negative sign was chosen when the resonance position in F_3CCOOH was in the lower field than that in CCl_4.

F_3CCOOH is very hygroscopic and therefore it was tried to be maintained dry throughout the preparation of the samples, but a small quantity of moisture or a moderate variation of the concentration of the measured substance from 5% seems not to have given any perceptible effect to the chemical shift.[*5] Total experimental error can be expected to be less than 0.02 p.p.m.

Results and Discussions

The differences of chemical shifts between in carbon tetrachloride and trifluoroacetic acid solutions are summarized in the Table and Figure.

Methyl, methylene and methin protons neighboured by carbonyl group which belong to ketone, aldehyde, acid and ester (except for amide) show almost same amount of the neutralizing downward shift, although their magnitudes are slightly different from each other depending on the type of the protons and on the kind of functional groups. With regard to methyl protons next to amide carbonyl, the shifts were considerably large as −0.56 and −0.75 as shown in the Table. It is interesting to note that they are larger than those shown by the protons attached directly to amide carbonyl,  $\underline{\mathrm{H}}\text{-}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\text{-N=}$.

As for the protons neighboured by an ether oxygen, methyl protons shifted downwards by −0.23 to −0.29, while the methylene and methin protons showed the shifts of ca. −0.4. The shifts differences of methylene groups belonging to benzyl or phenyl ether seem to be comparatively small, −0.3, and the ether methylene substituted by an amine function at β-position in the same molecule gave larger shifts of −0.56 and −0.69, compared with those of the usual ether methylene, as expected.

On the other hand, as for the protons neighboured by acetylated alcohol, $C\underline{H}\text{-}OCO\text{-}CH_3$, the magnitude of the shift differences fall between −0.12 and −0.24 and they are common to all types of protons, methyl, methylene or methin. It is interesting to mention that, while the significant difference was observed between the shift differences of methyl and methylene or methin of ethers, any difference was not found between those of esters.

The protons neighboured by amine group showed the largest shift of those of protons in any other kind. This can be easily understood by the fact that the amine

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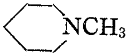
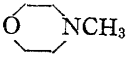
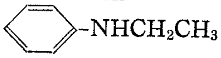
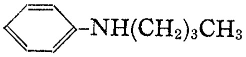
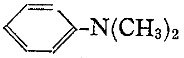
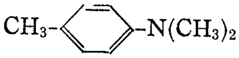
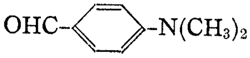
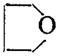
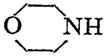
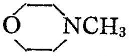
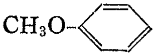
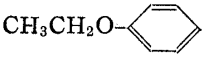
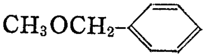
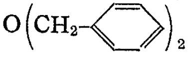
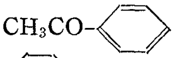
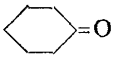
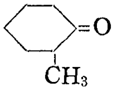
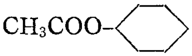
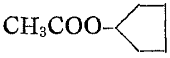
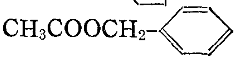
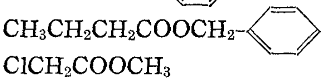
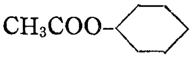
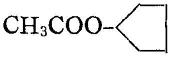
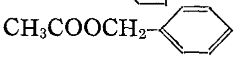
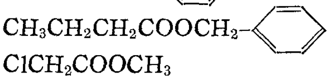
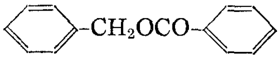
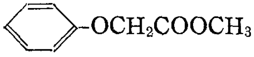
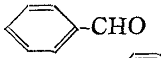
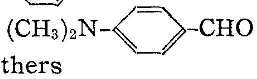
[*4] Since its signal appears at ca. −9.8 p.p.m. (ca. $-1.2\,\tau$) due to -COOH, it does not stain the spectrum.

[*5] The signal of the acidic proton of the solvent itself appears usually at ca. −9.8 p.p.m. from the reference. The position of this signal shifted upwards or downwards from −9.38 to −10.60, depending on the nature and concentration of the solutes.

Table I. Correlation of the Solvent Effect of Trifluoroacetic Acid with the Proton-types

R / Functional group	α-Position CH$_3$	α-Position CH$_2$	α-Position CH	Other position β-CH$_3$ or -CH$_2$
Alkyl amine				
$(CH_3CH_2)_2NH$		−0.70		−0.39
$(CH_3CH_2)_3N$		−0.90		−0.44
		−0.63		−0.40
	−0.76	−1.30		−0.42
		−0.82		−0.69
	−0.90	−1.33		−0.67
Aryl amine				
		−0.63		−0.24
		−0.60		
	−0.58			
	−0.57			
	−0.51			
Amide R-CON=				
$CH_3CONHCH_3$	−0.59			
	−0.75			
Amide -CON-R				
$CH_3CONHCH_3$	−0.46			
$HCON(CH_3)_2$	−0.41			
		−0.46		
$HCONH(CH_2CH_3)_2$		−0.41		−0.21
$(CH_3CH_2NH)_2CO$		−0.27		−0.11
Amide H-CON=				
$\underline{H}CON(CH_3)_2$				−0.53
$\underline{H}CON(CH_2CH_3)_2$				−0.45
Ether				
$CH_3OCH_2CH_2OH$	−0.28	−0.48		
$(CH_3CH_2)_2O$		−0.42		−0.13
$((CH_3)_2CHCH_2CH_2)_2O$		−0.44		
$((CH_3)_2CH)_2O$			−0.47	−0.23
$HOCH(CH_2OCH_2CH_3)_2$				−0.13
		−0.45		
		−0.39		−0.25
		−0.69		−0.82
		−0.67		−1.33
	−0.23			
		−0.30		−0.10
	−0.23	−0.29		
		−0.23		

Ketone				
CH_3COCH_3	-0.27			
$CH_3COCH_2CH_3$	-0.26	-0.29		-0.18
$CH_3COCH_2CH_2CH_3$	-0.27	-0.27		-0.13
 CH_3CO-	-0.26			
 =O		-0.29		
 =O CH_3				-0.12
Ester RCOO-				
$CH_3COOCH_2CH_3$	-0.22			
$CH_3COOCH(CH_3)_2$	-0.23			
 CH_3COO-	-0.22			
 CH_3COO-	-0.22			
 CH_3COOCH_2-	-0.20			
 $CH_3CH_2CH_2COOCH_2$-		-0.29		
$ClCH_2COOCH_3$		-0.19		
Ester -COOR				
$CH_3COOCH_2CH_3$		-0.23		-0.11
$CH_3COOCH(CH_3)_2$			-0.25	-0.13
 CH_3COO-			-0.22	
 CH_3COO-			-0.22	-0.12
 CH_3COOCH_2-		-0.19		
 $CH_3CH_2CH_2COOCH_2$-		-0.24		
$ClCH_2COOCH_3$	-0.15			
 -CH_2OCO-		-0.20		
 -OCH_2COOCH_3	-0.20			
Carboxylic acid				
CH_3COOH	-0.16			
CH_3CH_2COOH		-0.18		-0.08
$CH_3(CH_2)_2COOH$		-0.18		-0.08
$CH_3(CH_2)_{14}COOH$		-0.15		
Alkyl benzene				Ring proton
Benzene				-0.02
Toluene	+0.03			-0.08
o-Xylene	-0.01			-0.10
m-Xylene	+0.01			-0.12
p-Xylene	0.00			-0.12
p-Cymene	0.00		-0.04	-0.14
Tetraline		-0.02		-0.09
o-Nitrotoluene	-0.03			
o-Aminotoluene	-0.40			
p-Aminotoluene	-0.21			
p-Dimethylaminotoluene	-0.24			
Aldehyde	(-C$\underline{H}$O)			β-CH_3
$(CH_3)_2CHCHO$	-0.03		-0.23	-0.09
 -CHO	+0.05			
 $(CH_3)_2N$- -CHO	-0.43			
Others				
$Cl_2CHCHCl_2$			0.00	
$(CH_3)_4Si$	-0.02			

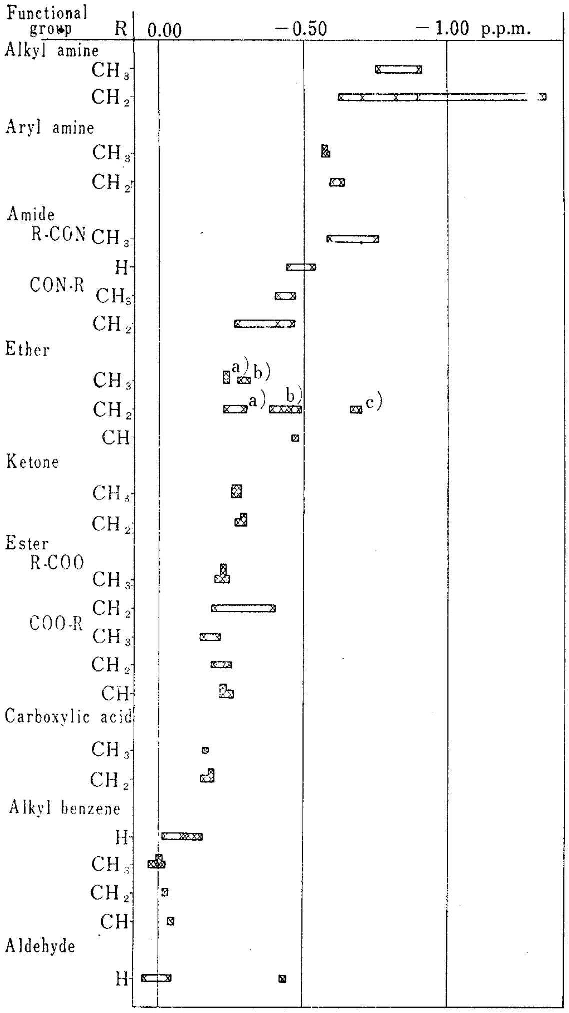


Fig. 1. Representation of Correlation of the Solvent Effect of Trifluoroacetic Acid with the Proton-type

a) Phenyl and benzyl ethers.
b) Aliphatic ethers.
c) β-Amino ethers.

group is so basic that the electronic character may be changed to the greater extent by the acidic reagent. The parallelism between the neutralizing shift and the basicity of the functional groups seems to have been proved in a rough sence. Thus, the shifts shown by aliphatic amines are always larger than those of aromatic amines and tertiary amines gave larger shift to methyl and methylene protons than secondary amines did.

Though trifluoroacetic acid affects the proton resonances to shift downwards as shown above, the protons of the alkyl group bonded to benzene ring did not show any remarkable neutralizing shift by this acid. Another case where no shift was brought out by this acid is the aldehyde protons, $-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\underline{\mathrm{H}}$. Although the samples examined were limited in number, it might be concluded that no shift would be caused with aldehyde proton, no matter whether it may be aliphatic or aromatic unless second functional group are also located in their neighbourhood.

In the case of benzene series, the shift differences of the ring protons of alkylbenzenes are about −0.1, while benzene itself gave no shift to ring protons. But amino, methoxyl or carbonyl groups seem to affect them to a greater extent, as shown in the Table.

In addition to the above results, it was observed that some examples whose protons was completely isolated from any functional group showed certain downward shifts of −0.05 to −0.12.

Further investigations should be needed for the detailed discussion on this solvent effect, which are now being studied in our laboratories.

Conclusion

The differences in the magnitude of the chemical shifts measured in two defferent solvents of carbon tetrachloride and strongly acidic trifluoroacetic acid were shown to be characteristic for each of various types of protons. This solvent effect may be supposed to be correlated with the basicities of the functional groups. Thus, in comparison of the protons of the type of CH–X, the neutralizing shifts tended to decrease in the following order :

aliphatic amine>aryl amine>aliphatic ether>phenolic ether>acylated alcohol.

On the other hand, protons of $C\underline{H}$–Cl, $C\underline{H}O$, phenyl$\underline{\text{alkyl}}$ and tetramethylsilane themselves did not show any difference in these two solvents.

In addition to its neutralizing effect as mentioned above, this solvent effect should be further considered in regard to many factors due especially to carbonyl and fluorine groups in the acid molecule.

The authors are indebted to Professor Toshihiko Okamoto of University of Tokyo and Dr. Chikara Kaneko of Tokyo Medical and Dental University for their encouragement and advices. They are also grateful to Drs. Osamu Yamamoto and Teruo Suzuki of the Government Chemical Industrial Research Institute of Tokyo for making a NMR spectrometer available for the present work.

Summary

The differences of the chemical shifts measured in two different solvents of carbon tetrachloride and trifluoroacetic acid were determined and tubulated with various kinds of compounds. The solvent effect of trifluoroacetic acid represented by the above chemical shift differences were characteristic for each proton-type. This fact may be applicable to the qualitative analysis of the compounds. It is also tried to correlate this solvent effect with the basicity of the functional group neighboured by the proton concerned.

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