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A SIMPLE DIAGNOSTIC METHOD OF AMINO FUNCTION OF ORGANIC COMPOUNDS USING NITROGEN-14 CHEMICAL SHIFTS

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Although the amino function of organic compounds can be characterized and identified by various methods such as pH titration, derivation, or colorimetric methods,[2] it is desirable to determine the amino function more conveniently. Problems of this type arise because all of primary, secondary and tertiary amines are often present in varying concentrations in the production of specific amines, and are therefore often contaminants in the amine products, especially when a very scantly amount of an amine from natural sources is available. ^{14}N chemical shift approach is expected to afford the fruitful information in this point, because it is sensitive to a slight extent of variation of electron distribution at the nitrogen atom. N-H proton signal is much subject to the influence of proton exchange and is unable to be used for this purpose.

Heteronuclear double resonance study of ^{14}N chemical shifts[3] has an advantage of greater sensitivity and accuracy in comparison with the direct method[4] when an appreciable nuclear spin coupling is included between proton and nitrogen atom of interest. The double resonance study, however, is hampered if the proton exchange rate is fast enough to decouple the proton from the nitrogen nucleus as in primary and secondary amines. This disadvantage is overcome by employing trifluoroacetic acid(TFA) as a solvent which is found to suppress significantly the rate of exchange of labile amine protons by protonation. A protonation of tertiary amines by TFA also enables us to perform the double resonance measurement of ^{14}N chemical shift accurately. In this letter we wish to report ^{14}N shifts of forty protonated amines and their application to qualitative analysis of mixed amines.

^{14}N nuclear double resonance is carried out with a Varian HA-100 spectrometer equipped with the probe doubly tuned to accept 7.22-MHz ^{14}N irradiation and

100-MHz proton observing frequencies. An NMR Specialties HD-60B heteronuclear spin decoupler equipped with a Hewlett-Packard 200 ABR audiofrequency oscillator was used to drive the 7.22-MHz irradiation frequency. All measurements were carried out in the frequency-sweep mode with a small amount of TMS added to samples for field-frequency stabilization. A sample of 4.5M NH_4NO_3 in 3N aqueous hydrochloric acid was used as a reference for ^{14}N shifts.[3b] The details are the same as in our previous papers.[3c,3d] For the diagnostic usage it is necessary to determine the optimum concentration in which ^{14}N shift is characteristic of the amino function, since ^{14}N shifts have been found to depend upon solvents and concentrations.[3c,3d,5] Examination of concentration dependency of n-propylamines revealed that ^{14}N shifts retain the constant value below 0.2 mole fraction in TFA. We performed the measurements at 0.05 mole fraction to obtain the shift in a better signal to noise ratio. The accuracy of the measurements is within ±0.5 ppm. ^{14}N shifts thus obtained are tablulated in Table I. The ^{14}N resonance peaks are shown to extend over 53 ppm for protonated amines. This contrasts with 2.6 ppm spread observed in N-H proton shifts. It should eventually be possible to use these larger ^{14}N shifts relative to proton shifts for the present purpose.

Table I shows that the ^{14}N shifts of the same alkyl substituents are shifted downfield with the number of substituents as follows.

$$\text{Primary}\ -\overrightarrow{(12-26)}\text{ppm}\quad \text{Secondary}\ -\overrightarrow{(8-13)}\text{ppm}\quad \text{Tertiary}$$

In the case of methyl group, the above values are replaced by -3.0 and -2.0 ppm, respectively. This trend appears to be a consequence of -I inductive effect of alkyl group.[6] Increased alkylation results in a decrease of electron density at the nitrogen atom, which is accompanied by the downfield shift of ^{14}N chemical shift. ^{14}N shifts of straight-chain substituent, however, is not always varied monotonically with the number of carbon atoms in the substituent attached to the nitrogen atom. Similar trend is denoted by ^{13}C shift of a series of alkanes[7] which is described as γ effect.

A relatively larger difference of ^{14}N shifts makes it possible to observe the individual chemical shifts in a mixture of different amines, as shown in the following example. ^{14}N spectrum of mixed primary, secondary and tertiary

Table I. ^{14}N shifts of protonated amines(TFA solution,ppm)

Substituent	Primary		Secondary		Tertiary	
	$\delta_{NH_4^+}$ [a]	$\delta_{NO_3^-}$ [b]	$\delta_{NH_4^+}$ [a]	$\delta_{NO_3^-}$ [b]	$\delta_{NH_4^+}$ [a]	$\delta_{NO_3^-}$ [b]
CH_3	+0.8	354.3(351)[c]	-1.9	351.6(348)[c]	- 4.2	349.3(334)[c]
CH_3CH_2	-18.0	335.5(336)[c]	-30.5	323.0(320)[c]	-39.5	314.0(314)[c]
$CH_3(CH_2)_2$	-7.2	346.3	-26.3	327.2	-36.7	316.8
$CH_3(CH_2)_3$	-9.7	343.8	-25.6	327.9	-33.9	319.5
$CH_3(CH_2)_4$	-11.2	342.3	-25.8	327.7	-34.0	319.5
$CH_3(CH_2)_5$			-27.4	326.1		
$CH_3(CH_2)_{17}$	-11.8	341.7				
$(CH_3)_2CH$	-28.4	325.1	-52.2	301.3		
$(CH_3)_2CHCH_2$	-15.5	338.0	-21.3	332.2		
$(CH_3)_3C$	-37.4	316.1(314)[c]				
$(CH_3)_2CH(CH)_2$	-12.7	340.8	-24.9	328.6	-37.8	315.7
CH_2=$CHCH_2$	-12.7	340.8	-27.4	326.1	-37.9	315.6
Cyclohexyl	-25.5	328.0	-51.6	301.9		
	-25.8	327.7				
	-17.2	336.3			-45.8	307.7
			-24.2	329.3		
			-19.4	334.1		
			-14.9	338.6		
$H_2NCH_2CH_2$	-9.4	344.1				
$H_2N(CH_2)_3$	-9.4	344.1				
$H_2N(CH_2)_6$	-10.9	342.6				
$H_2N(CH_2)_{10}$	-11.8	341.7				

[a] ^{14}N shift referred to ammonium ion(±0.5 ppm). [b] ^{14}N shift referred to nitrate ion, $\delta_{NO_3^-} = \delta_{NH_4^+} + 353.5 \pm 0.5$.[c] [c] Reference 4b.

n-propylamines (mole ratio, 2:3:6, respectively) is shown in Figure 1(A). A broad curve with three maxima is resolved into three components of approximately same intensities, each of which corresponds to three kinds of n-propylamines traced separately (Figure 1(B)), by a trial-and-error method. An N-H proton peak, on the other hand, shows a singlet peak indicating a rapid proton exchange process among three kinds of amines.[8] This observation clearly indicates that ^{14}N shift method should be used as a convenient vehicle for the rapid analysis of amino function even in the mixed state. An application of ^{14}N shift for

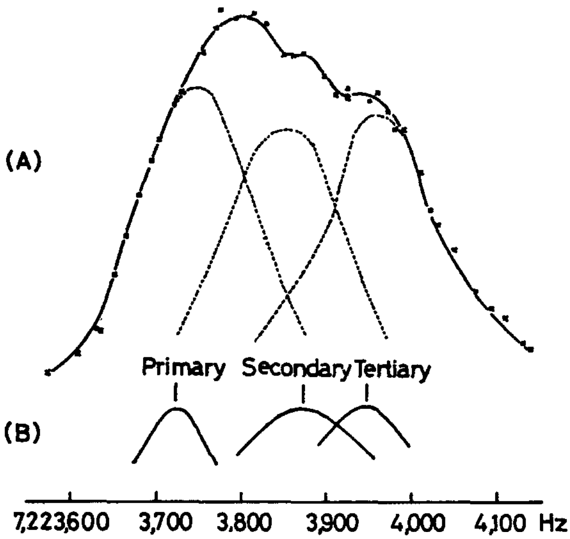

Figure 1

^{14}N spectra of n-propylamines in CF_3COOH solution recorded by plotting N-H proton peak intensities against the ^{14}N irradiation frequencies.

(A) Mixtures of primary-, secondary and tertiary-n-propylamines with 2:3:6 mole ratio, respectively.

(B) The same components are recorded separately.

the analysis of mixed amines has recently been carried out to observe the cross-linkage by tertiary amines caused by the thermal degradation of polyamides.[10]

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(8) A condition to observe signals separately in an exchange state is describedby the following formula:[9] $k < \pi/\sqrt{2}\cdot(\delta_A - \delta_B)$, where k stands for the rate constant of proton exchange, and δ_A and δ_B are chemical shifts of site A and B in frequency unit. In the case of Figure 1, we obtain the range of the rate constant: 38Hz(proton shifts)$<$ k $<$170Hz(^{14}N shifts).

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