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NMR SPECTRAL STUDIES—XII

TRICHLOROACETYL ISOCYANATE AS AN *IN SITU* DERIVATIZING REAGENT FOR ^{13}C NMR SPECTROSCOPY OF ALCOHOLS, PHENOLS AND AMINES[1]

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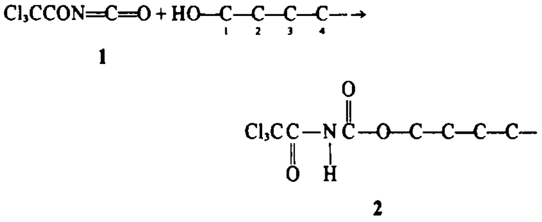
Abstract—Trichloroacetyl isocyanate (TAI) has been found to be a useful *in situ* derivatizing reagent for the ^{13}C NMR studies on alcohols, phenols and amines. The carbinol carbon of aliphatic alcohols shows downfield shifts the size of which permits distinction between primary, secondary and tertiary saturated alcohols. In allylic and propargylic alcohols the γ-carbon undergoes large downfield shifts while the β-carbon is shifted upfield. In the case of phenols, the OH-bearing carbon is shifted upfield, the *o*- and *p*-carbons are shifted downfield but *m*-carbons are virtually unaffected. Addition of TAI to amines and anilines produces various size shifts for the α- and β-carbons. The use of TAI is thus a valuable aid in the assignment of the resonance signal of a carbon carrying an OH or NH-group as well as some neighboring carbons in ^{13}C NMR spectra for structural and biosynthetic studies.

Trichloroacetyl isocyanate (TAI) was suggested as an *in situ* derivatizing reagent for proton NMR studies of alcohols by Goodlett[2] in 1965. The usefulness of TAI was illustrated by work done in our laboratory[3] on a variety of sterols. Since then limited use has been made of this reagent in PMR studies of several types of natural products.[4-6] Recently we have examined the value of TAI for ^{13}C NMR of alcohols and amines. We wish to report now that TAI can provide valuable aid in the assignment of the resonance signal of a carbon carrying a hydroxy or an amino group as well as some of the neighboring carbons in ^{13}C NMR spectra.

^{13}C NMR studies on alcohols. The addition of TAI (1) to a solution of an alcohol in chloroform, carbon tetrachloride or other nonhydroxylic solvents causes an immediate exothermic reaction to take place leading to the formation of an urethane (2).



$$\mathrm{Cl_3CCON{=}C{=}O} + \mathrm{HO}-\underset{1}{\mathrm{C}}-\underset{2}{\mathrm{C}}-\underset{3}{\mathrm{C}}-\underset{4}{\mathrm{C}}- \rightarrow$$

1

$$\mathrm{Cl_3C}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{\underset{\mathrm{H}}{|}}{\mathrm{N}}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{O}-\mathrm{C}-\mathrm{C}-\mathrm{C}-\mathrm{C}-$$

2

This reaction can be carried out in an NMR tube and the ^{13}C NMR spectrum of the sample rerecorded. The three new carbons so introduced resonate at lower magnetic field than chloroform (*ca.* 92, 150 and 152 ppm downfield from TMS) as do the C atoms of the unreacted TAI. A comparison of the broad-band proton decoupled ^{13}C NMR spectra of the sample before and after the addition of TAI shows that only a few resonance peaks have been shifted.

On the basis of a modest number of different types of alcohols studied, the following generalizations could be made about the effect of reaction with TAI:

Saturated alcohols. TAI-induced shifts for a variety of saturated alcohols are listed in Table 1 along with the chemical shifts for the appropriate C atoms of the parent alcohol.

The carbinol carbon (C-1) is shifted downfield by 3–16 ppm. It appears possible to distinguish between the three types of alcohols on the basis of the size of the shift to lower magnetic field:

primary alcohols: 3·5–5·5 ppm
secondary alcohol: 6·0–8·0 ppm
tertiary alcohol: 10·0–16·0 ppm

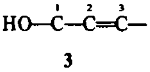
It is interesting to note that in proton NMR spectra a similar distinction is possible[2,3] on the basis of the downfield shift of the proton attached to the carbinol carbon, upon addition of TAI:

primary alcohol: 0·5–0·9 ppm
secondary alcohol: 0·9–1·5 ppm
tertiary alcohol: ——

The C-2 carbon adjacent to the carbinol carbon is shifted upfield by 4·0–5·0 ppm. The magnitude of this shift is decreased with branching at that carbon; thus, C-2 is shifted upfield by 3·13 ppm in 2-methylpropanol and by only 1·08 ppm in 2,2-dimethylpropanol. The carbons that are farther away (C-3, C-4, etc.) are shifted upfield by less than 1 ppm.

Shifts observed for a series of alcohols upon their conversion into acetates have been reported by Lippmaa and Pehk;[7] downfield shifts for the C-1 carbons (1·0–2·8 ppm) were not diagnostic of the type of alcohol studied. A few instances of upfield shifts of 3·5–5·2 ppm for the C-2 carbons have also been reported by these workers. However, conversion of an alcohol into its acetate involves a separate experiment and consequent delay and inconvenience. Highly hindered alcohols may resist acylation. One advantage of TAI is that it reacts almost instantaneously with any alcohol including hindered carbinols.[3] This reaction can be carried out conveniently in an NMR sample tube; a moderate excess of the reagent does not cause any difficulty in recording the ^{13}C NMR spectra.

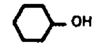
Unsaturated alcohols. Under this category allylic (3), propargylic (4) and benzylic (5) alcohols have been studied:



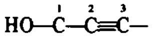
$$\mathrm{HO}-\overset{1}{\mathrm{C}}-\overset{2}{\mathrm{C}}{=}\overset{3}{\mathrm{C}}-$$

3

Table 1. TAI-induced shifts in the ^{13}C NMR spectra of saturated alcohols

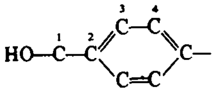
		Chemical shifts & TAI-induced shifts[a]			ppm
Sl. No.	Alcohol	C_1	C_2	C_3	C_4
1	$\overset{2}{C}H_3\overset{1}{C}H_2OH$	(57.94) + 5.40	(18.24) - 4.1		
2	$\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}H_2OH$	(64.22) + 4.42	(26.26) - 4.1	(10.57) - 0.11	
3	$\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2OH$	(62.47) + 4.64	(35.07) - 4.53	(19.21) - 0.33	(13.92) - 0.33
4	$(CH_3)_2CH\ CH_2OH$	(69.49) + 3.77	(30.86) - 3.13	(18.88) 0.00	
5	$(CH_3)_3C\ CH_2OH$	(72.29) + 4.53	(32.59) - 1.08	(26.00) - 0.33	
6	$(CH_3)_2CHOH$	(63.88) + 7.98	(25.25) - 3.56		
7	$(CH_3CH_2)_2CHOH$	(74.67) + 6.36	(29.67) - 3.45	(10.03) - 0.64	
8		(70.14) + 6.36	(35.61) - 4.32	(25.68) - 0.98	(24.39) - 0.43
9	$(CH_3)_3\text{-}C\text{-}OH$	(68.95) +15.64	(31.29) - 3.34		
10	$(CH_3)_2\text{-}\underset{OH}{C}H\text{-}CH_2CH_3$	(71.21) +15.97	(36.47) - 3.13 (CH_2) (28.70) - 3.45 (CH_3)	(8.74) - 0.65	

[a] Numbers in parenthesis against each compound represent chemical shifts of the carbon atoms in ppm downfield from TMS; values below the chemical shifts are the TAI-induced shifts. +ve denotes shift to lower magnetic field.



$HO\text{—}\overset{1}{C}\text{—}\overset{2}{C}{\equiv}\overset{3}{C}\text{—}$

4



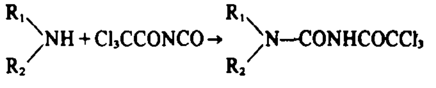
5

In all these cases the carbinol carbon (C-1) is shifted downfield but the range of shift is about 2·5–4·5 ppm irrespective of whether primary, secondary or tertiary alcohols are involved.

For these alcohols, the C-2 is shifted upfield by about 4·5–7·0 ppm while C-3 is shifted downfield-in some propargylic alcohol by as much as 11 ppm. These shifts would thus help distinguish the unsaturated C atoms.

The observations on a variety of unsaturated hydroxy compounds are listed in Table 2 along with chemical shifts of the carbons of the parent compounds.

Amines. TAI reacts exothermally with solutions of amines also; in the case of primary and secondary amines, substituted ureas of type (6) are formed.



6

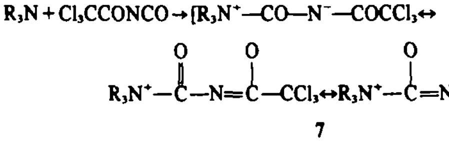
(R_1=H or Alkyl)

Table 2. TAI-induced shifts in the ^{13}C NMR spectra of allylic and propargylic alcohols

		Chemical shifts & TAI-induced shifts[a]			ppm
Sl. No.	Alcohol	C_1	C_2	C_3	C_4
1	$\overset{3}{C}H_2{=}\overset{2}{C}H\overset{1}{C}H_2OH$	(63.66) + 3.99	(137.60) - 6.80	(115.13) + 4.75	
2	$CH_3CH{=}CHCH_2OH$	(63.23) + 4.53	(130.67) - 6.69	(128.51) + 4.75	(17.59) + 0.21
3	$C_6H_5\overset{3}{C}H{=}\overset{2}{C}HCH_2OH$	(63.44) + 4.43	(127.64) - 6.25	(130.99) + 4.74	(136.82) - 0.65
4		(64.74) + 4.10	(141.03) - 6.59	(127.3) + 0.32	(127.00) + 1.72
5	$\overset{3}{C}H{\equiv}\overset{2}{C}\text{—}\overset{1}{C}H_2OH$	(50.49) + 2.81	(82.32) - 5.07	(73.90) + 4.32	
6	$\overset{3}{C}H{\equiv}\overset{2}{C}\text{—}\underset{OH}{\overset{1}{C}}HCH_2CH_2CH_3$	(62.04) + 2.48	(85.34) - 5.40 (39.81) - 3.35 (CH_2)	(72.83) + 4.96 (18.45) - 0.43 (CH_2)	
7	$\overset{3}{C}H{\equiv}\overset{2}{C}\text{-}\underset{OH}{\overset{1}{C}}\text{—}(CH_3)_2$	(54.27) + 3.99	(89.01) - 5.61 (31.40) - 2.48 (CH_3)	(70.24) +10.68	
8	$\overset{3}{C}H{\equiv}\overset{2}{C}\text{—}\underset{CH_3}{\overset{OH}{\overset{1}{C}}}\text{—}CH_2CH_3$	(68.52) + 3.67	(87.83) - 5.61 (36.36) - 2.05 (CH_2) (29.13) - 3.34 (CH_3)	(71.32) -10.79 (8.85) - 0.43 (CH_3)	

[a] See footnote below Table 1.

Tertiary amines also react with TAI forming probably derivatives of type 7:



$$R_3N + Cl_3CCONCO \rightarrow [R_3N^+—CO—N^-—COCCl_3 \leftrightarrow R_3N^+—\overset{O}{C}—N{=}\overset{O}{C}—CCl_3 \leftrightarrow R_3N^+—\overset{O}{C}{=}N—COCCl_3]$$

7

As in the case of alcohols, the three new carbons of the TAI derivative (6) appear at *ca.* 92, 151, and 162 ppm downfield from TMS. In the case of tertiary amines, only the signal at 92δ (due to —$\underline{C}Cl_3$) is seen; the two downfield resonances are not clearly seen probably because the two C atoms concerned have a different relaxation time due to contributions from the reasonance structure 7.

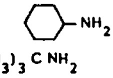
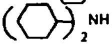
Conversion of an amine into its TAI derivative generally causes a shift of the C atom bearing the amino group (C-1) and its neighbor (C-2). C-1 shifts are of the order of 1·0–4·0 ppm upfield for primary and secondary amines with the exception of some C-1 branched amines wherein the magnitude of the shift falls off and even changes direction to downfield. For tertiary amines, C-1 shifts are smaller and can be in either direction. However, in the case of all types of aliphatic amines, C-2 is shifted upfield by 2·0–5·0 ppm. Carbons more remote show small upfield shifts of 0·0–1·5 ppm. TAI-induced shifts observed for a variety of amines are listed in Table 3; for the sake of ready reference, the ^{13}C chemical shifts for these amines before addition of TAI are also included.

Phenols and aromatic amines. Phenols and aromatic amines belong to a separate class. For phenols, reaction with TAI causes the OH-bearing carbon to shift upfield by 5–6 ppm and the *ortho* and *para* carbons to shift downfield by 5–6·5 ppm; *meta* carbons undergo negligible shift. In the case of aromatic amines, the carbon bearing the amino function is shifted upfield by 5–15 ppm while the *ortho* and *para* carbons are shifted downfield by 5·5–15·5 ppm; as with phenols, *meta* carbons are practically unaffected. Secondary aryl-alkyl amines produce large downfield shifts (~6–7 ppm) for the aliphatic C-1 carbon atoms. While substituent effects in monosubstituted benzenes reported in literature[8] might help identification of the different aromatic carbons in such compounds, di-, tri- or poly-substituted phenols and aryl amines may pose problems in correct ^{13}C spectral assignments; TAI-induced shifts for such compounds may prove valuable. Table 4 shows the TAI-induced shifts for a variety of phenols and aromatic amines.

TAI in ^{1}H NMR of amines. As the effect of addition of TAI on the proton NMR spectra of amines did not appear to have been investigated so far, we examined this aspect also. A study of different kinds of amines showed that the protons in the vicinity of the amino function undergo downfield shift, the magnitude of this shift falling off with distance. The following general changes and shifts are noticed in the ^{1}H NMR spectra of amines upon addition of TAI:

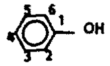
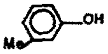
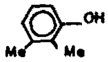
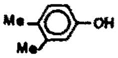
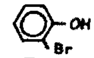
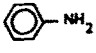
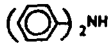
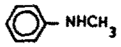
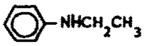
1. One amino proton of primary amines and the secondary amino proton disappear and a new resonance due to the NH proton in the TAI derivative 6 appears as a broad signal in the 8·5–9·0 δ region.
2. Primary and secondary amines show a downfield shift of 0·6–0·8 ppm for the C-1 protons, which decreases in magnitude with increased branching at C-1.
3. Protons on C-2 show downfield shifts of 0·1–0·4 ppm for primary amines and 0·1–0·2 ppm for secondary amines.
4. Protons on C-3 and remote carbons show shifts of less than 0·1 ppm.
5. Tertiary amines show larger downfield shifts

Table 3. ^{13}C chemical shifts and TAI-induced shifts for Amines

		C-13 chemical shifts & TAI-induced shifts[a] ppm			
Sl. No.	Compound	C_1	C_2	C_3	C_4
1	$\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}H_2NH_2$	(45.35) -3.27	(27.08) -4.42	(11.64) -0.11	
2	$CH_3CH_2CH_2CH_2NH_2$	(42.19) -2.16	(36.25) -4.85	(20.18) -0.22	(14.03) -0.33
3	$(CH_3)_2CHNH_2$	(42.84) 0.00	(26.22) -3.67		
4	$CH_3CH_2-\underset{CH_3}{CH}-NH_2$	(48.56) -0.44	(33.02) -3.35 (23.63) -3.45 (CH_3)	(10.68) -0.43	
5		(50.60) -1.18	(37.12) -4.53	(25.25) -0.76	(25.90) -0.33
6	$(CH_3)_3\,C\,NH_2$	(47.37) +4.42	(32.59) -3.78		
7	$(CH_3)_2CHCH_2NH_2$	(50.39) -2.81	(31.72) -3.34	(20.07) -0.11	
8	$(CH_3CH_2)_2NH$	(44.13) -1.62	(15.43) -2.16		
9	$(CH_3CH_2CH_2)_2NH$	(52.01) -2.27	(23.52) -2.26	(11.87) -0.65	
10		(47.58) -1.08	(27.41) -1.73	(25.25) -1.30	
11		(46.61) -0.64	(68.19) -2.16		
12		(53.41) +4.64	(34.53) -3.99	(26.33) -0.11	(25.46) -0.11
13	$(CH_3CH_2)_3N$	(46.50) +4.46	(12.87) -4.35		
14	$(CH_3CH_2CH_2)_3N$	(56.54) +0.97	(20.50) -3.67	(11.98) -0.76	
15	$(CH_3CH_2CH_2CH_2)_3N$	(57.62) -0.94	(29.46) -4.32	(20.82) -0.75	(14.13) -0.54

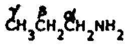
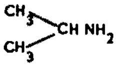
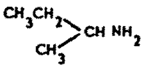
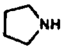
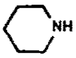
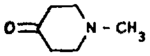
[a] See footnote below Table 1.

Table 4. TAI-induced shifts in the ^{13}C NMR spectra of phenols and aromatic amines

		C-13 chemical shifts & TAI-induced shifts[a]				(ppm)	
Sl. No.	Compound	C_1	C_2	C_3	C_4	C_5	C_6
1		(155.36) - 5.50	(115.55) + 5.50	(129.79) - 0.11	(120.84) +5.83	(129.79) - 0.11	(115.55) + 5.50
2		(155.04) - 5.40	(121.92) + 5.39	(139.93) - 0.21	(116.31) + 5.28	(129.58) - 0.44	(112.64) + 5.39
3		(153.42) - 5.07	(123.97) + 5.72	(138.42) + 0.32	(122.56) + 5.50	(126.02) + 0.11	(123.97) + 6.04
4		(151.37) - 5.18	(130.01) + 6.26	(131.73) + 0.11	(123.97) + 5.29	(127.42) 0.00	(115.01) + 6.04
5		(153.20) - 5.50	(116.84) + 5.07	(137.99) 0.00	(128.82) + 6.04	(130.55) - 0.22	(112.42) + 5.50
6		(152.23) - 5.39	(110.26) + 5.40	(132.17) + 1.18	(121.81) + 6.26	(129.04) - 0.44	(116.31) + 7.12
7		(145.52) - 9.13	(115.02) + 5.72	(129.26) - 0.11	(118.37) + 5.79	(129.26) - 0.11	(115.02) + 5.72
8		(143.19) -15.33	(117.93) + 9.18	(129.37) + 0.43	(117.93) + 5.72	(129.37) + 0.43	(117.93) + 9.18
9		(149.54) - 8.42 (29.95) + 6.90 (CH_3)	(112.42) +14.46	(129.25) + 0.86	(117.17) +11.65	(129.25) + 0.86	(112.42) +14.46
10		(148.47) - 9.17 (38.30) + 6.59 (CH_2)	(112.76) +15.42 (14.78) - 1.72 (CH_3)	(129.16) + 1.51	(117.07) +12.10	(129.16) + 1.51	(112.76) +15.42

[a] See footnote below Table 1.

Table 5. TAI-induced shifts in the proton NMR spectra of amines in $CDCl_3$ solutions

		Downfield shifts			(ppm)
Sl. No.	Amine	α-CH	β-CH	γ-CH	δ-CH
1	 $\overset{\gamma}{C}H_3\overset{\beta}{C}H_2\overset{\alpha}{C}H_2NH_2$	0.66	0.21	0.07	
2	$CH_3CH_2CH_2CH_2NH_2$	0.66	*	*	0.04
3	$(CH_3)_2CHCH_2NH_2$	0.68	0.38	0.07	
4		0.93	0.14		
5		1.07	0.13	0.06	
6	$(CH_3)_3\,CNH_2$	—	0.27		
7	$(CH_3CH_2)_2NH$	0.78	0.12		
8	$(CH_3CH_2CH_2)\ NH$	0.70	0.16	0.04	
9		0.67	0.14		
10		0.67	0.14	0.18	
11	$(CH_2CH_2)_3N$	0.87	0.26		
12	$(CH_3CH_2CH_2)_3N$	0.85	0.22	0.12	
13	$(CH_3CH_2CH_2CH_2)_3N$	0.83	*	*	0.07
14		0.62 (CH_3) 0.95 (CH_2)	0.40		

*Signals not resolved.

(0·8–0·9 ppm) for the C-1 protons and shifts of 0·2–0·3 ppm for the C-2 protons.

Table 5 shows the TAI-induced shifts in the PMR spectra of representative types of different kinds of amines.

Some phenols and aromatic amines form TAI derivatives which are less soluble than the parent compounds. On the other hand, the advantages afforded by TAI for the study of alcohols are that the urethanes are highly soluble in common NMR solvents and that because of its linear molecular shape, it reacts almost instantaneously with even highly hindered OH groups.[3]

EXPERIMENTAL

All ^{13}C NMR spectra reported here were recorded by Pulse Fourier Transform on a Bruker HX-90 NMR spectrometer employing an external F-19 lock or an internal H-2 lock and broad-band proton decoupling (90 MHz); an operating frequency of 22·638 MHz was used for the ^{13}C nucleus and TMS was used as internal reference; ^{13}C chemical shifts are δ values relative to TMS (0·0 ppm).

All alcohols, phenols and amines were of reagent grade; alcohols and phenols were used as such and the amines were dried over KOH before use.

Trichloroacetyl isocyanate (TAI), a product of Eastman Kodak, (grade not specified) was purchased from Fisher Scientific Co. In a typical study, the PFT C-13 spectrum of the alcohol or amine (300–500 mg) in $CDCl_3$ was first recorded. The sample tube was then cooled in a bath of ice-water and then TAI added drop by drop until there was no more effervescence. (Insufficient additions of TAI could be recognized by two sets of resonances in the spectrum, one due to the parent compound and the other due to the TAI derivative). The ^{13}C spectrum of this TAI derivative soln was rerecorded.

^{13}C chemical shifts for most of the compounds examined here are already reported[9] in literature; where necessary, techniques of off-resonance and single-frequency proton decoupling were adopted to help unambiguous assignments. Proton NMR spectra were recorded on a Varian A-60 A NMR spectrometer with TMS as internal reference. Spectra of amine solutions in $CDCl_3$ were observed before and after addition of TAI.

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