CORRELATION BETWEEN ^{13}C CHEMICAL SHIFTS AND REACTIVITY OF HETEROAROMATIC NITRILES: A NEW REACTIVITY INDEX, γ, FOR THE CONDENSATION REACTION WITH ENOLATE ANION OF ACETONE

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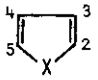
Abstract —— ^{13}C nmr studies of various heteroaromatic nitriles revealed an interesting correlation between a value composed of the chemical shifts, $\delta_{\underline{C}N}$ and $\delta_{\underline{C}-CN}$, and the reactivity of the nitriles in forming the corresponding enaminoketones through the reactions with enolate anion of acetone. Based on the correlation, a new reactivity index, γ, is proposed.

A useful method of preparing the enaminoketones from which a variety of heterocycles can be derived has been reported by Honma and Tada.[1] The method is a condensation reaction between the nitrile and the enolate anion of ketone shown in the following scheme.[2]

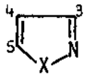
$$R\text{-}CN + R^1\text{-}CH_2\text{-}CO\text{-}R^2 \xrightarrow{NaNH_2/ether} R\text{-}C(NH_2)=C(R^1)\text{-}CO\text{-}R^2$$

Many heteroaromatic nitriles have been converted into the corresponding enaminoketones by this method.[1,2] However, there are heteroaromatic nitriles inactive in this reaction. A series of substituted benzonitriles and simple aliphatic nitriles also do not give the enaminoketones. The reactivity greatly depends upon the R group of R-CN.

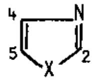
Through ^{13}C nmr studies of heteroaromatic and aromatic nitriles, we found an interesting correlation between the reactivity and the value composed of $\delta_{\underline{C}N}$ and $\delta_{\underline{C}-CN}$, which are the ^{13}C chemical shift of the cyano carbon and that of the carbon bearing the cyano group, respectively. ^{13}C signal assignments of the compounds (1-45) examined are listed in the Table together with the reactivity grades and γ values, which will be defined later. According to the relative rate of the condensation reaction at 0°C using nitrile, acetone, and sodium amide, in a mole ratio of 1:2:2, and anhydrous ether as a solvent, the reactivity grade was roughly classified into grades A-D; to complete the reaction, compounds of grades A, B, or C required a very short time (a few minutes), *ca*. 10-30 min, or over 1 h, respectively, while compounds of grade D were inactive or gave only by-products.



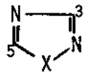
	X	2	3
1:	O	CN	
2:	O		CN
3:	N-Ph	CN	
4:	N-Ph		CN
5:	S	CN	
6:	S		CN



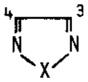
	X	3	4	5
7:	O	CN		Me
8:	O	Me	CN	Me
9:	O	Me		CN
10:	S	CN		Me
11:	S	Me	CN	
12:	S	Me		CN
13:	N-Ph	CN		Me
14:	N-Ph		CN	
15:	N-Ph	Me		CN



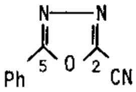
	X	2	4	5
16:	O	CN		Me
17:	O	Me	CN	Me
18:	O	Me	Me	CN
19:	S	CN		
20:	S	Me	CN	
21:	S	Me		CN



	X	3	5
22:	O	CN	Ph
23:	O	Ph	CN
24:	N-Ph	CN	
25:	N-Ph		CN



	X	3	4
26:	O	CN	Me
27:	S	CN	
28:	N-Ph	CN	



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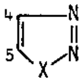
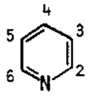
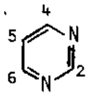


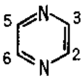
	X	4	5
30:	N-CH_2Ph	CN	Me
31:	N-Ph		CN



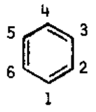
	2	3	4
32:	CN		
33:		CN	
34:			CN



	2	4	5	6
35:	CN			
36:	Me	CN		Me
37:	Me	Me	CN	



	2	3
38:	CN	
39:	CN	Me



	1	4
40:	CN	
41:	CN	NO_2
42:	CN	CN
43:	CN	Cl
44:	CN	OMe
45:	CN	NMe_2

TABLE. ^{13}C Chemical Shifts (δ),[a] Reactivity Index, and Reactivity Grade of Compounds **1**-**45**

Compound No.	γ[b]	R.G.[c]	CN	C-1	C-2	C-3	C-4	C-5	C-6	Other C
1	+27.6	B	111.7	-	126.4	122.2	111.7	147.5	-	-
2	-6.8	D	113.0	-	149.8	97.2	111.0	144.1	-	-
3	+5.4	D	111.6	-	103.8	121.9	110.5	126.8	-	Ph: 123.8, 128.0, 129.5, 138.0
4	-21.7	D	116.2	-	126.3	95.1	113.3	121.2	-	Ph: 121.2, 127.5, 129.9, 139.1
5	+1.7	C	114.0	-	109.7	132.3	127.4	137.3	-	-
6	-1.1	D	114.9	-	135.3	110.5	128.5	127.3	-	-
7	+46.3	B	110.3	-	-	139.5	104.2	172.9	-	Me: 12.1
8	-3.3	D	110.9	-	-	159.7	92.3	176.6	-	Me: 10.3, 12.3
9	+55.5	B	108.7	-	-	160.7	114.7	142.3	-	Me: 11.1
10	+31.5	B	113.9	-	-	139.1	126.6	166.9	-	Me: 12.8
11	+5.3	D	113.0	-	-	167.6	109.3	157.0	-	Me: 17.8
12	+38.0	B	110.8	-	-	167.4	131.5	133.2	-	Me: 18.7
13	+16.1	C	114.2	-	-	124.9	111.4	140.9	-	Me: 12.1, Ph: 124.9, 129.0, 129.3, 138.4
14	-9.9	D	113.0	-	-	142.9	94.1	131.9	-	Ph: 119.5, 127.9, 129.5, 138.5
15	+17.4	C	111.1	-	-	149.9	115.6	113.8	-	Me: 13.2, Ph: 122.4, 128.3, 129.3, 138.5
16	+47.2	B	109.1	-	135.6	-	126.0	154.5	-	Me: 11.2
17	+8.5	D	112.6	-	160.8	-	110.9	158.0	-	Me: 11.2, 13.6
18	+30.1	B	109.7	-	164.5	-	149.4	120.9	-	Me: 12.2, 14.2
19	+33.2	B	112.8	-	136.4	-	145.2	125.6	-	-
20	+17.5	D	114.1	-	168.0	-	125.9	130.8	-	Me: 19.1
21	+6.6	D	111.7	-	171.8	-	151.8	105.4	-	Me: 19.4
22	+62.4	A	108.5	-	-	148.4	-	177.7	-	Ph: 122.1, 128.3, 129.5, 134.2
23	+75.0	A	106.1	-	-	169.2	-	151.4	-	Ph: 124.4, 127.5, 129.0, 132.3
24	+40.7	B	111.8	-	-	139.9	-	142.3	-	Ph: 120.3, 129.5, 129.9, 135.8
25	+39.5	B	109.3	-	-	152.7	-	128.7	-	Ph: 122.8, 129.9, 130.1, 135.6
26	+51.8	B	107.5	-	-	133.8	152.9	-	-	Me: 8.1
27	+35.8	B	111.5	-	-	133.8	152.7	-	-	-
28	+25.7	B	111.2	-	-	122.5	129.3	-	-	Ph: 119.4, 129.5, 138.7, 139.2
29	+64.7	A	106.2	-	141.5	-	-	166.5	-	Ph: 121.7, 127.6, 129.4, 133.3
30	+21.1	C	111.9	-	-	-	120.7	140.7	-	Me: 8.4, CH_2:52.4, Ph: 127.4, 128.7, 129.1, 133.2
31	+25.0	B	108.5	-	-	-	140.3	111.0	-	Ph: 120.3, 129.7, 130.5, 134.8
32	+12.4	B	117.3	-	133.6	128.5	138.4	127.0	151.6	-
33	-10.1	D	117.0	-	152.9	109.9	140.5	123.6	152.2	-
34	+3.1	C	116.3	-	150.6	125.2	120.3	125.2	150.6	-
35	+29.8	B	115.8	-	145.0	-	158.2	124.1	158.2	-
36	+25.7	B	115.8	-	169.5	-	140.9	120.9	169.2	Me: 24.3, 25.9
37	-5.1	D	114.8	-	170.4	-	169.7	106.1	159.6	Me: 23.4, 26.4
38	+17.2	D	115.4	-	130.8	148.3[d]	-	147.6[d]	145.5	-
39	+16.0	D	115.5	-	130.0	157.8	-	146.4	142.7	Me: 21.7
40	-14.4	D	118.7	112.4	131.9	129.1	132.7	129.1	131.9	-
41	-0.5	D	116.7	118.3	133.4	124.2	150.1	124.2	133.4	-
42	-3.2	D	117.0	116.8	132.6	132.6	116.8	132.6	132.6	CN: 117.0
43	-11.9	D	117.7	110.9	133.3	129.6	139.3	129.6	133.3	-
44	-24.6	D	119.1	103.8	133.8	114.8	162.9	114.8	133.8	OMe: 55.5
45	-36.7	D	120.4	96.9	133.0	111.3	152.3	111.3	133.0	NMe: 39.7

[a] ^{13}C FT nmr spectra were measured with a Varian NV-14 FT nmr spectrometer at 15.087 MHz in 8-mm tubes at 30°C. Samples were dissolved in $CDCl_3$ containing TMS as an internal reference; concentrations were *ca.* 1 mmol/cm^3. Measurement conditions: spectral width, 3017 Hz; pulse width, 10 μsec (90° pulse: 62 μsec); acquisition time, 0.6 sec; number of data points, 3706; and number of transients, 3000. ^{13}C signals were assigned using single-frequency off-resonance decoupling (SFORD) techniques,[3] δ_C values reported for analogous compounds,[3,4a-f] known substituent effects,[3] and indirect ^{13}C, ^{1}H coupling features;[3,5a-c] in some cases, Eu(fod)$_3$ was applied in combination with the SFORD technique.[3,6] [b] Reactivity index (see text). [c] Reactivity grade (see text). [d] These assignments may be exchanged.

The Table shows that the grade A compounds have $\delta_{\underline{\mathrm{C}}\mathrm{N}}$ smaller than 109 and that the compounds having $\delta_{\underline{\mathrm{C}}\mathrm{N}}$ larger than 118 do not give the enaminoketones; this implies a compound having smaller $\delta_{\underline{\mathrm{C}}\mathrm{N}}$ is more reactive. However, the reactivity is not correlated with $\delta_{\underline{\mathrm{C}}\mathrm{N}}$ only, as indicated by the variety of reactivities in compounds having an intermediate $\delta_{\underline{\mathrm{C}}\mathrm{N}}$ value ($109 \lesssim \delta_{\underline{\mathrm{C}}\mathrm{N}} \lesssim 118$). At the same time, a reverse correlation was found between $\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}}$ and the reactivity. The compounds having $\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}}$ larger than 133 exhibit good reactivity, but all compounds with a $\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}}$ smaller than 108 do not give the enaminoketones; this implies the larger the $\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}}$, the more reactive the compound is.

Finding no clear relationship between the ^{13}C chemical shifts of the other carbons and the reactivity, we constructed a correlation diagram between the chemical shifts, $\delta_{\underline{\mathrm{C}}\mathrm{N}}$ and $\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}}$, of compounds and the reactivity grade, as shown in Fig. 1. The regions of the reactivity grades are divided by parallel linear lines 1, 2, and 3. These lines are represented by the following Eqs. 1, 2, and 3, respectively.

$$\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}} = 4\delta_{\underline{\mathrm{C}}\mathrm{N}} - 348 \qquad (1)$$

$$\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}} = 4\delta_{\underline{\mathrm{C}}\mathrm{N}} - 324 \qquad (2)$$

$$\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}} = 4\delta_{\underline{\mathrm{C}}\mathrm{N}} - 290 \qquad (3)$$

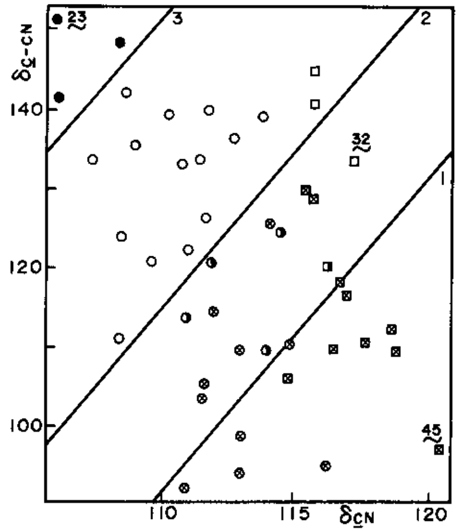


Fig. 1. Diagram of the correlation between reactivity grade and ^{13}C chemical shifts, $\delta_{\underline{\mathrm{C}}\mathrm{N}}$ and $\delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}}$, of nitriles.[a]

[a] 5-membered ring system: ●, grade A; ○, grade B; ◑, grade C; and ⊗, grade D.
6-membered ring system: □, grade B; ◧, grade C; and ⊠, grade D.

Here, we define the reactivity index, γ, using Eq. 4.

$$\gamma = \delta_{\underline{\mathrm{C}}\text{-}\mathrm{CN}} - 4\delta_{\underline{\mathrm{C}}\mathrm{N}} + 348 \qquad (4)$$

This γ value can be used to classify the reactivity of nitriles as follows: $\gamma \gtrsim 62$ (highly reactive); $62 \gtrsim \gamma \gtrsim 24$ (reactive); $24 \gtrsim \gamma \gtrsim 0$ (less reactive or inactive: ambiguous); $\gamma < 0$ (inactive).[7] The following limitations, however, should be noted. A compound with a considerably acidic proton is easily converted into a conjugated anion under the reaction conditions and will show low reactivity even if its γ value lies in a reactive region; this is the reason we used compounds protected by the methyl or phenyl group whenever possible. Similarly, a compound unstable due to side reactions, such as ring cleavage, does not give the objective enaminoketone in good yield regardless of its γ value. An extremely low solubility of the nitrile will also retard the progress of the reaction. More strictly, application of this γ rule should be distinguished between 5- and 6-membered ring systems because of their different ring strain, π-conjugation, etc., which to some extent are reflected in their ^{13}C nmr behavior. The anomaly of 32 found in the γ rule may be due to this.

MO calculations[4b,8] for a series of substituted benzonitriles and 2-, 3-, or 4-cyanopyridines indicated that π-electron density or total electron density of cyano carbons are almost constant in each series. Our MO calculations for various nitriles[9] using PPP-SCF, EH, and CNDO/2 methods confirmed a general tendency that the change in electron density on the cyano carbon of the molecules is very small. No clear correlation was found between the electron density and $\delta_{\underline{C}N}$, although we found the interesting tendency that a nitrile having a small $\delta_{\underline{C}N}$ exhibits low LUMO energy. This tendency was seen in both 5- and 6-membered ring systems (see Fig. 2). At present, we can not clearly explain its physical meaning, since we have not evaluated the contribution of electronic transitions to which the lowest-lying excited state is related and that of the other factors influencing the ^{13}C screening constant.[11] In view of the reactivity, however, the

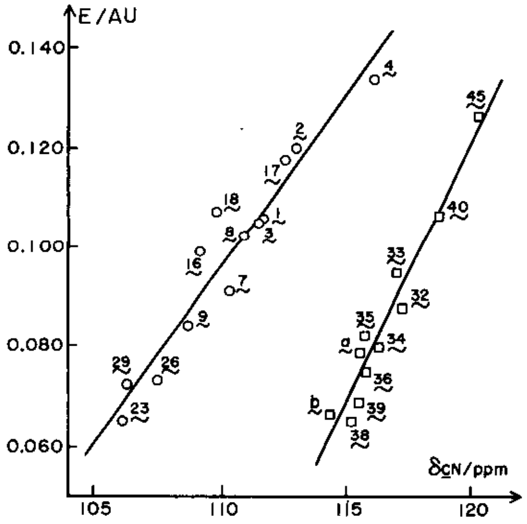
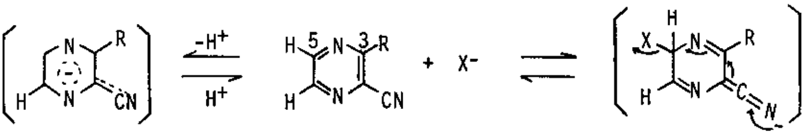


Fig. 2. Correlation between $\delta_{\underline{C}N}$ and LUMO energy calculated by CNDO/2. [a],[b]

[a] ○, 5-membered ring system ; □, 6-membered ring system.

[b] Compounds a and b are 3-cyanopyridazine and 4-cyanopyridazine, respectively [10]

role of LUMO seems to be important when we consider the large contribution of the interaction between the LUMO of nitrile and the HOMO of enolate anion in initiating the reaction.[9,12] Accordingly, we can accept the tendency of a nitrile having a smaller $\delta_{\underline{C}N}$ (*viz*. lower LUMO energy) being more reactive. In spite of the very low LUMO energy, however, the reaction of **38** or **39** resulted in recovery of the starting material. This is presumably due to the proton on C-5 or C-3 being acidic enough to be abstracted by the base or the C-5 or C-3 being activated far more than the cyano carbon; in any case, the progress of the objective reaction is prevented, as shown below. These



(R = H or Me)

examples make it evident that the reaction is not simply controlled by the LUMO energy alone.[13]

A significant change in electron density on the $\underline{C}$-CN depending upon the compound was shown by the MO calculations, and a tendency for the $\underline{C}$-CN having a higher positive charge to exhibit a larger $\delta_{\underline{C}-CN}$ was found.[14] As a higher positive charge on the $\underline{C}$-CN assists approach of the enolate anion to the reactive site, $\underline{C}$N, the contribution of $\delta_{\underline{C}-CN}$ to the reactivity index, γ, seems reasonable.

Although its theoretical foundation is incomplete, the empirical γ rule proposed here should be useful for predicting the reactivity of analogous molecules in analogous reactions.

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7. Undoubtedly, this reactivity index should be convenient for organic chemists, but raises the problem that some may come to only request ^{13}C nmr measurements and not investigate the reaction. Such a situation reminded us of the convenient but dangerous γ-rays and led to the naming of this reactivity index.
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9. M. Yamakawa, T. Kubota, Y. Terui, T. Honma, and Y. Tada, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3059.
10. Because of side reactions, such as ring cleavage, the corresponding enaminoketones were not obtained from these compounds.
11. With simple molecules in which heteroaromatic nitriles were not involved, Webb and coworkers reported the evaluation of contributions to the paramagnetic component of the ^{13}C screening tensor from various electronic transitions by using the CNDO/S or INDO/S method on the approximation of the second-order perturbation theory (K. A. K. Ebraheem and G. A. Webb, *Org. Magn. Reson.*, 1977, **9**, 241; M. Jallali-Heravi and G. A. Webb, *Org. Magn. Reson.*, 1978, **11**, 34). To explain δ_{CN} behavior found in substituted alkanenitriles, Yonemoto proposed the importance of π-bond polarization in the cyano group on the basis of his calculations (T. Yonemoto, *J. Magn. Reson.*, 1973, **12**, 93), but also pointed out the anomaly found for the nitriles having *sp*^{2}-hybridized α-carbon, such as benzonitrile. With

substituted benzonitriles, a correlation between $\delta_{\underline{C}N}$ and Hammet σ (or σ^+) has been reported by Inamoto *et al.*,[4f] though all of these compounds do not give the enaminoketones.

12. K. Fukui, T. Yonezawa, and C. Nagata, *Bull. Chem. Soc. Jpn.*, 1954, **27**, 423.
13. Besides the orbital energy, the MO coefficient at each atom in the molecule is also important when the reactivity is considered.[9,12]
14. An approximately linear correlation between the electron density and $\delta_{\underline{C}\text{-}CN}$ found in a series of substituted benzonitriles has been reported.[4b]

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