

# Determination of Aromaticity Indices of Thiophene and Furan by Nuclear Magnetic Resonance Spectroscopic Analysis of Their Anilides

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A series of *m*- and *p*-substituted anilides of benzoic acid, 2-thienoic acid, and 2-furoic acid were prepared and their  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectroscopic characteristics were examined. In general, good correlations were observed between the chemical shifts of proton and carbon signals of the acyl aromatic rings and the Hammett  $\sigma$ . Plots of the chemical shift values of the carbonyl carbons of the benzanilides against those of the 2-thienamides and 2-furamides gave an excellent correlation and the values of the slopes are 0.79 and 0.52, respectively, in dimethyl sulfoxide- $d_6$ . The slopes could be considered as a set of aromaticity index.

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Aromaticity is one of the most important concepts in organic chemistry. The concept, which was originated to explain the unique physical and chemical nature of benzene, has been extended to a rather wide range of phenomena. Quantification of aromaticity has been a subject of numerous research papers. Five-membered monoheterocyclic compounds such as thiophene, pyrrole and furan have been frequently cited as aromatic heterocycles due to the fact that they possess  $6\pi$  electrons. However, the quantification of their aromaticity has been based on the relative magnitude of observable physical properties such as resonance energy, bond length, or ring current [1,2]. For example, comparison of the ring current provides the indices of aromaticity of benzene, thiophene, pyrrole, and furan as 1.00, 0.75, 0.59, and 0.46, respectively [3]. Consideration of bond length gives a different set of indices: benzene 1.00, thiophene 0.93, pyrrole 0.91, and furan 0.87 [4]. A statistical evaluation of the deviations in peripheral bond orders suggests benzene 100, thiophene 66, pyrrole 59, and furan 43 [5].

In a previous paper we reported that the chemical shift values of *m*- and *p*-substituted phenyl esters could be used for estimation of aromaticity [6]. The method is based on the observation of good correlation of the chemical shift values with the Hammett  $\sigma$ . Comparison of the slope of the correlation with the benzene derivatives to thiophene or furan derivatives should provide a relative magnitude of aromaticity. We have extended the method to *m*- and *p*-substituted anilides of benzoic acid, 2-thienoic acid, and 2-furoic acid.

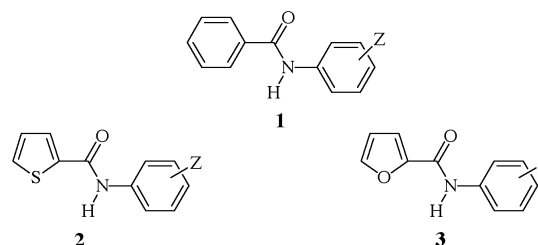
Correlation of  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  chemical shifts of substituted benzanilides with the Hammett  $\sigma$  has been reported [7,8]. Effect of substituents on the chemical shifts of the azomethine carbon atom of *N*-benzylideneanilines and 2-*N*-arylimino-2-*p*-nitrophenylethanenitriles has also been investigated [9]. The chemical shifts of the carbonyl group, in the type of  $\text{XC}_6\text{H}_4\text{COZ}$  ( $\text{Z} = \text{NH}_2, \text{F}, \text{OEt}, \text{OH}, \text{Me}, \text{H}$ ), have also been studied [10]. A theoretical investigation of the  $\pi$  polarization mechanism has also been carried out to explain the effect of substituent on the

chemical shifts of the carbonyl system [11]. However, there has been no systematic investigation on the nature of the aromaticity of the 5-membered heteroaromatic compounds by examining the correlation of chemical shift values and substituent constants.

Here we report our extensive examination of the correlation of the chemical shift values of *m*- and *p*-substituted anilides and their correlation with relative aromaticity of thiophene and furan.

## Results and Discussion.

The *m*- and *p*-substituted anilides (**1-3**) were prepared by the condensation of acyl chlorides with *m*- and *p*-substituted anilines in triethylamine.



Purification of the products was done by repeated recrystallization from ethanol or silica gel chromatography to obtain materials of analytical purity. The chemical shifts were found to be dependent on concentration as shown in Table 1. Therefore, analytical purity of each compound is essential for the accurate preparation of the 0.1 M solution used in our spectral analyses.

The amides **1-3** are soluble enough to prepare 0.1-1.0 M solution in dimethyl sulfoxide- $d_6$ , but are not soluble enough in chloroform to make even a 0.1 M solution. Yuzuri *et al.* employed solutions of pyridine, acetone, methanol, acetonitrile, and dimethyl sulfoxide at the

Table 1  
Slopes (in Hz) and Correlation Coefficients of the Plots of  $^1\text{H}$  and  $^{13}\text{C}$   
Chemical Shift Values  
of **1k**, **2k**, and **3k** vs. Concentrations (0.01-1.0 *M*) in Dimethyl Sulfoxide- $d_6$

	<b>1k</b>		<b>2k</b>		<b>3k</b>	
	slope	r	slope	r	slope	r
N-H	26.4	0.999	29.5	0.999	27.3	0.999
N-H'	61.3	0.999	-		79.7	0.993
<i>o</i> -H	24.4	0.999	26.5	0.999	20.3	0.987
<i>m</i> -H	1.7	0.673	5.1	0.971	3.9	0.964
<i>p</i> -H	-2.1	0.904	-4.4	0.927	4.8	0.963
<i>o'</i> -H	33.2	0.999	32.2	0.999	32.7	0.999
<i>m'</i> -H	9.2	0.995	10.6	0.997	13.7	0.996
<i>p'</i> -H	7.0	0.996	8.0	0.995	11.3	0.975
C=O	8.5	0.998	9.3	0.999	9.7	0.997
<i>i</i> -C	9.9	0.999	10.5	0.999	11.4	0.997
<i>o</i> -C	5.9	0.999	3.6	0.995	5.1	0.996
<i>m</i> -C	-1.7	0.954	-2.3	0.971	1.2	0.957
<i>p</i> -C	-3.0	0.990	-9.2	0.999	-0.7	0.997
<i>i'</i> -C	9.0	0.999	6.7	0.998	6.3	0.997
<i>o'</i> -C	8.4	0.999	8.7	0.998	9.6	0.999
<i>m'</i> -C	1.4	0.951	0.9	0.932	1.9	0.987
<i>p'</i> -C	1.8	0.974	2.2	0.967	4.5	0.993

concentration of "about 100 mg of an anilide in about 0.6 ml of solvent" which should correspond to 0.5-0.8 *M* for their investigation [8]. These solvents have relatively high dielectric constants. The solvent effect may not be significantly different, except in the case of pyridine, which can act as a base. Therefore, we obtained the spectra only in dimethyl sulfoxide- $d_6$  at 0.1 *M* to maintain consistency among our data.

The  $^1\text{H}$  and  $^{13}\text{C}$  nmr chemical shift values of the amides **1-3** are listed in Tables 2 and 3, respectively. Accurate assignment of each peak was possible by analyzing  $^1\text{H}$ - $^1\text{H}$  COSY and  $^1\text{H}$ - $^{13}\text{C}$  HETCOR spectra. In addition, correlations of the chemical shift values of 2-thienoyl and 2-furoyl compounds against those of benzoyl compounds (*cf.* Table 5) make the assignments unambiguous. The correlations of each proton and carbon peak in *m*- and *p*-substituted phenyl rings (not listed) show slopes of near unity with correlation coefficient of 0.999-1.000. This could also be used to make accurate assignments.

Table 2  
 $^1\text{H}$  Chemical Shift Values of Substituted Anilides **1-3** in Dimethyl Sulfoxide- $d_6$  (0.1 *M*)

	NH	NH'	<i>o</i> -H	<i>m</i> -H	<i>p</i> -H	2'-H	3'-H	4'-H	5'-H	6'H
<b>1a</b>	10.71	3.33	8.01	7.56	7.62	8.82		8.21	7.67	7.97
<b>1b</b>	10.40	3.34	7.96	7.55	7.62	8.12		7.30	7.33	7.77
<b>1c</b>	10.41	3.32	7.96	7.55	7.62	7.99		7.17	7.39	7.73
<b>1d</b> [a]	10.22	3.32	7.95	7.53	7.60	7.49		7.39	7.25	6.69
<b>1e</b> [a]	10.17	3.32	7.95	7.53	7.59	7.63		6.92	7.23	7.56
<b>1f</b>	10.82	3.32	7.99	7.57	7.65	8.08	8.28			
<b>1g</b>	10.37	3.32	7.95	7.54	7.61	7.54	7.78			
<b>4h</b>	10.38	3.32	7.95	7.54	7.61	7.83	7.42			
<b>1i</b> [a]	10.12	3.32	7.95	7.52	7.58	7.68	6.93			
<b>1j</b> [a]	10.16	3.32	7.95	7.52	7.58	7.66	7.16			
<b>1k</b>	10.25	3.32	7.96	7.53	7.60	7.79	7.53	7.10		
<b>2a</b>	10.67	3.33	8.08	7.27	7.93	8.73		8.18	7.66	7.97
<b>2b</b>	10.36	[b]	8.03	7.25	7.89	8.05		7.30	7.33	7.73
<b>2c</b>	10.38	[b]	8.04	7.25	7.89	7.92		7.17	7.39	7.68
<b>2d</b> [a]	10.19	[b]	8.03	7.23	7.86	7.42		7.32	7.26	6.69
<b>2e</b> [a]	10.14	[b]	8.03	7.22	7.85	7.56		6.93	7.23	7.53
<b>2f</b>	10.76	[b]	8.11	7.28	7.95	8.03	8.28			
<b>2g</b>	10.34	[b]	8.03	7.24	7.88	7.54	7.72			
<b>2h</b>	10.35	[b]	8.03	7.24	7.88	7.77	7.42			
<b>2i</b> [a]	10.12	[b]	7.98	7.21	7.83	7.62	6.93			
<b>2j</b> [a]	10.15	[b]	8.01	7.22	7.84	7.60	7.16			
<b>2k</b>	10.23	[b]	8.03	7.23	7.86	7.73	7.36	7.11		
<b>3a</b>	10.66	3.32	7.42	6.75	8.00	8.77		8.19	7.65	7.96
<b>3b</b>	10.33	3.32	7.36	6.73	7.96	8.08		7.30	7.32	7.75
<b>3c</b>	10.35	3.31	7.36	6.72	7.96	7.94		7.16	7.38	7.70
<b>3d</b> [a]	10.14	3.32	7.33	6.71	7.94	7.44		7.36	7.24	6.68
<b>3e</b> [a]	10.07	3.32	7.33	6.70	7.93	7.59		6.92	7.22	7.55
<b>3f</b>	10.75	3.33	7.46	6.76	8.01	8.05	8.26			
<b>3g</b>	10.31	3.32	7.35	6.72	7.95	7.53	7.75			
<b>3h</b>	10.32	3.32	7.35	6.71	7.95	7.78	7.38			
<b>3i</b> [a]	10.06	3.33	7.29	6.69	7.91	7.65	6.92			
<b>3j</b> [a]	10.08	3.32	7.31	6.69	7.92	7.63	7.14			
<b>3k</b>	10.17	3.31	7.34	6.71	7.94	7.75	7.34	7.10		

[a]  $\text{CH}_3$ : **1d**, 3.76; **1e**, 2.31; **1i**, 3.75; **1j**, 2.28; **2d**, 3.76; **2e**, 2.31; **2i**, 3.75; **2j**, 2.28; **3d**, 3.75; **3e**, 2.30; **3i**, 3.74; **3j**, 2.27; [b] Not observed.

Table 3

<sup>13</sup>C Chemical Shift Values of Substituted Anilides **1-3** in Dimethyl Sulfoxide-*d*<sub>6</sub> (0.1 M). Values in Parenthesis are the Difference of the Chemical Shift between the Major and the Minor Rotamers with the Negative Sign Indicating the Upfield Shift

	C=O	<i>i</i> -C	<i>o</i> -C	<i>m</i> -C	<i>p</i> -C	1'-C	2'-C	3'-C	4'-C	5'-C	6'-C
<b>1a</b>	166.54 (-0.05)	134.87 (-0.05)	128.26	129.00	132.53	140.86 (-0.11)	114.82 (-0.09)	148.39	118.60	130.54	126.64 (-0.09)
<b>1b</b>	166.29 [b]	135.04 [b]	128.20	128.95	132.32	141.30 [b]	123.31 (-0.09)	121.91	126.73	131.13	119.49 (-0.10)
<b>1c</b>	166.30 (-0.08)	135.05 (-0.05)	128.18	128.93	132.30	141.15 (-0.10)	120.17 (-0.09)	133.42	123.81	130.80	119.09 (-0.09)
<b>1d</b> [a]	166.07 (-0.09)	135.45 (-0.04)	128.12	128.86	132.05	140.86 (-0.10)	106.50 (-0.10)	159.91	109.63	129.86	113.02 (-0.10)
<b>1e</b> [a]	165.95 (-0.08)	135.50 (-0.04)	128.10	128.85	131.98	139.57 (-0.10)	121.38 (-0.10)	138.22	124.82	128.91	118.02 (-0.10)
<b>1f</b>	166.76 [b]	134.70 [b]	128.40	129.00	132.66	145.98 [b]	120.30 [b]	125.27	142.94		
<b>1g</b>	166.14 (-0.34)	135.18 (-0.05)	128.16	128.90	132.20	139.06 (-0.12)	122.68 (-0.10)	131.91	115.80		
<b>1h</b>	166.14 (-0.08)	135.19 (-0.05)	128.16	128.90	132.19	138.64 (-0.10)	122.31 (-0.10)	129.00	127.73		
<b>1i</b> [a]	165.57 (-0.09)	135.53 (-0.04)	128.01	128.82	131.84	132.71 (-0.09)	122.45 (-0.11)	114.21	156.02		
<b>1j</b> [a]	165.81 (-0.08)	135.53 (-0.04)	128.07	128.82	131.91	137.12 (-0.10)	120.86 (-0.10)	129.46	133.06		
<b>1k</b>	166.04 (-0.09)	135.48 (-0.05)	128.13	128.86	132.02	139.66 (-0.10)	120.84 (-0.10)	129.08	124.14		
<b>2a</b>	160.83 (-0.08)	139.62 (-0.10)	130.64	128.74	133.20	139.62 (-0.03)	114.77 (-0.09)	148.40	118.63	130.32	126.54 (-0.09)
<b>2b</b>	160.54 (-0.13)	139.97 [b]	130.00	128.65	132.85	139.97 (-0.06)	123.01 (-0.11)	121.93	126.78	131.19	119.44 (-0.09)
<b>2c</b>	160.60 [b]	139.99 [b]	130.02	128.67	132.86	139.99 [b]	120.19 [b]	133.49	123.91	130.90	119.09 [b]
<b>2d</b> [a]	160.38 [b]	140.41 [b]	129.59	128.56	132.43	140.41 [b]	106.49 [b]	159.93	109.75	129.59	113.02 [b]
<b>2e</b> [a]	160.30 (-0.06)	140.65 (-0.05)	129.49	128.55	132.29	138.26 (-0.05)	121.40 (-0.17)	139.12	124.93	129.00	118.04 (-0.07)
<b>2f</b>	160.92 (-0.10)	139.52 (-0.06)	130.76	128.77	133.57	145.61 (-0.20)	120.26 (-0.10)	125.34	142.80		
<b>2g</b>	160.45 [b]	140.17 [b]	129.87	128.62	132.67	138.64 (-0.10)	122.71 (-0.10)	132.01	115.95		
<b>2h</b>	160.45 [b]	140.17 [b]	129.85	128.61	132.64	138.21 (-0.08)	122.35 (-0.10)	129.10	127.87		
<b>2i</b> [a]	160.03 [b]	140.75 (-0.05)	129.20	128.50	131.98	132.17 [b]	122.55 (-0.09)	114.30	156.12		
<b>2j</b> [a]	160.19 [b]	140.70 [b]	129.34	128.52	132.16	136.65 (-0.13)	120.92 (-0.16)	129.56	133.22		
<b>2k</b>	160.38 (-0.10)	140.56 (-0.05)	129.60	128.57	132.36	139.21 (-0.11)	120.89 (-0.11)	129.18	124.26		
<b>3a</b>	157.02 (-0.09)	147.37 (-0.05)	116.12	112.85	146.76	140.30 (-0.11)	114.82 (-0.09)	148.38	118.63	130.56	126.62 (-0.10)
<b>3b</b>	156.78 (-0.09)	147.59 (-0.06)	115.72	112.75	146.50	140.68 (-0.10)	123.01 (-0.09)	121.88	126.77	130.12	119.49 (-0.10)
<b>3c</b>	156.81 (-0.19)	147.61 (-0.05)	115.74	112.76	146.50	140.55 (-0.10)	120.18 (-0.10)	133.42	123.88	130.82	119.12 (-0.10)
<b>3d</b> [a]	156.69 [b]	147.97 [b]	115.24	112.65	146.22	140.21 [b]	106.59 [b]	159.90	109.67	129.91	113.05 [b]
<b>3e</b> [a]	156.64 (-0.05)	148.03 (-0.05)	115.06	112.58	146.14	138.92 (-0.10)	121.37 (-0.10)	138.27	124.91	128.95	118.04 (-0.09)
<b>3f</b>	157.01 (-0.08)	147.28 (-0.08)	116.57	112.92	147.00	145.46 (-0.12)	120.30 (-0.08)	125.27	142.97		

Table 3 (continued)

<sup>13</sup>C Chemical Shift Values of Substituted Anilides **1-3** in Dimethyl Sulfoxide-*d*<sub>6</sub> (0.1 M). Values in Parenthesis are the Difference of the Chemical Shift between the Major and the Minor Rotamers with the Negative Sign Indicating the Upfield Shift

	C=O	<i>i</i> -C	<i>o</i> -C	<i>m</i> -C	<i>p</i> -C	1'-C	2'-C	3'-C	4'-C	5'-C	6'-C
<b>3g</b>	156.71 (-0.07)	147.76 (-0.05)	115.55	112.71	146.38	138.44 (-0.10)	112.70 (-0.10)	131.94	115.93		
<b>3h</b>	156.71 (-0.08)	147.76 (-0.04)	115.53	112.71	146.37	138.02 (-0.10)	122.33 (-0.11)	129.04	127.85		
<b>3i</b> [a]	156.44 (-0.10)	148.20 (-0.04)	114.76	112.56	145.79	131.99 (-0.09)	122.49 (-0.10)	114.26	156.10		
<b>3j</b> [a]	156.55 (-0.09)	148.11 (-0.06)	114.93	112.56	146.02	136.45 (-0.09)	120.87 (-0.10)	129.49	133.19		
<b>3k</b>	156.68 (-0.04)	148.00 (-0.04)	115.18	112.62	146.17	139.00 (-0.10)	120.85 (-0.10)	129.11	124.21		

[a] CH<sub>3</sub>: **1d**, 55.48; **1e**, 21.71; **1i**, 55.65; **1j**, 20.97; **2d**, 55.50; **2e**, 21.67; **2i**, 55.67; **2j**, 20.98; **3d**, 55.49; **3e**, 21.68; **3i**, 55.66; **3j**, 20.95; [b] Not observed.

The substituent effects, on the chemical shift of nuclei in an aromatic compound, are typically analyzed by the single substituent parameter (SSP) and dual substituent parameter (DSP) approach, which are represented by Equations 1 and 2, respectively [12].

$$\delta = \rho\sigma + \delta_o \quad (1)$$

$$\delta = \rho_I\sigma_I + \rho_R\sigma_R + \delta_o \quad (2)$$

Although DSP analysis shows good correlation, we have found that SSP analysis is suitable for the purpose of our examination. The results of substituent correlation are listed in Table 4. The positions 2, 3, 4, and 5 of the heterocyclic ring can be defined as *ipso*, *ortho*, *meta*, and *para* to the carbonyl group, respectively. Such representation has been used throughout the present report.

Table 4

Best Fit of the Single Substituent Parameter Equation for <sup>1</sup>H and <sup>13</sup>C Chemical Shifts of **1-3** in Dimethyl Sulfoxide-*d*<sub>6</sub> (0.1 M) in Hz

	<b>1</b>		<b>2</b>		<b>3</b>	
	$\rho$	$r$	$\rho$	$r$	$\rho$	$r$
<i>o</i> -H	18.90	0.856	37.01	0.909	53.70	0.964
<i>m</i> -H	18.72	0.984	23.79	0.988	25.15	0.981
<i>p</i> -H	23.98	0.972	43.39	0.993	36.83	0.992
N-H	255.91	0.967	240.08	0.962	265.37	0.966
$\rho_{o-H}/\rho_{p-H}$	0.79		0.85		1.46	
C=O	95.3	0.979	75.8	0.986	50.3	0.976
<i>i</i> -C	-90.4	0.974	-125.1	0.993	-89.0	0.992
<i>o</i> -C	29.0	0.949	144.9	0.989	157.0	0.987
<i>m</i> -C	18.9	0.987	25.2	0.989	34.6	0.990
<i>p</i> -C	75.3	0.994	137.0	0.989	93.0	0.987
$\rho_{o-C}/\rho_{p-C}$	0.38		1.06		1.69	

The plot of the chemical shifts of benzoyl protons and carbons against those of the 2-thienoyl and 2-furoyl analogs may be correlated to the relative magnitude of the magnetic property of each ring. This is especially true with the chemical shift of carbonyl carbon, as shown in Figure 1, because the carbon is under the direct influence of the ring current of the aryl or heteroaryl ring. The slopes and correlation coefficients of such plots are listed in Table 5.

As shown in Table 5, the slopes for carbonyl carbons are 0.79 ( $r = 0.995$ ) and 0.52 ( $r = 0.984$ ) for thiophene and furan, respectively. The correlation is excellent with the thiophene series, indicating that the rings of thiophene and benzene may behave very similarly. Therefore, the slope of 0.79 may be taken as the value of aromaticity index of thiophene when that of benzene is set at 1.00. Similar rationale indicates that the aromaticity index of furan is 0.52, although the correlation is not as closely matched with that of benzene as the thiophene series. The values of the indices are fairly close to those reported in literature based on the ring current [3].

Table 4 and Figure 2 show that the correlations of the chemical shift against the Hammett  $\sigma$  are, in general, fair to good for all protons and carbons except the *ortho*-Hs of **1-3**. The *ortho*-Hs show merely a trend of correlation, and the poorest correlation was observed with the *ortho*-H of **1** ( $r = 0.856$ ).

One striking observation in Table 4 is the uniquely reversed correlation of the *ipso*-carbon against the Hammett  $\sigma$ . Reversed correlation of the substituent effect on the chemical shift of this carbon atom has been well documented in the literature. For example, Brownlee, *et al.* reported reverse <sup>13</sup>C substituent chemical shift effect in the side-chain carbon of a series of benzoyl derivatives, X-C<sub>6</sub>H<sub>4</sub>-C(Y)=O (Y = NH<sub>2</sub>, F, OEt, OH, Me, H) where the electron-withdrawing substituents X caused upfield shifts of the carbonyl carbon [10]. This observation is attributed

Table 5  
Slopes and Correlation Coefficients of the Plots of  $^1\text{H}$  and  $^{13}\text{C}$  Chemical Shift Values of the Benzanilides (**1**) vs. Those of the *N*-Phenyl-2-thiophenecarboxamides (**2**) and *N*-Phenyl-2-furanamide (**3**) in Dimethyl Sulfoxide- $d_6$

	Thiophene		Furan			Thiophene		Furan	
	slope	r	slope	r		slope	r	slope	r
N-H	0.94	0.999	1.04	0.999	C=O	0.79	0.995	0.52	0.984
<i>o</i> -H	1.46	0.872	1.98	0.861	<i>i</i> -C	1.45	0.988	1.03	0.989
<i>m</i> -H	1.12	0.999	1.21	0.995	<i>o</i> -C	4.61	0.962	5.10	0.980
<i>p</i> -H	1.57	0.994	1.34	0.997	<i>m</i> -C	1.31	0.988	1.78	0.976
					<i>p</i> -C	1.82	0.996	1.31	0.989

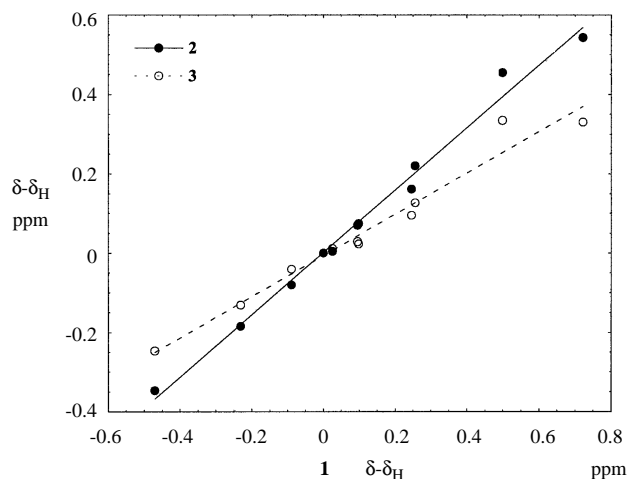


Figure 1. Plot of  $^{13}\text{C}$  chemical shifts of carbonyl carbon in **2** and **3** against those in **1**.

to  $\pi$ -polarization. The magnitude of such effect decreases in cases of substituted phenylacetic acids and substituted phenyl acetates because the methylene group and oxygen atom cause the carbonyl carbon and the substituent to be farther apart.

Suezawa, *et al.* examined the substituent effect on  $^1\text{H}$ ,  $^{15}\text{N}$ , and  $^{13}\text{C}(=\text{O})$  chemical shifts of ten *m*- and *p*-substituted benzanilides ( $\text{X}-\text{C}_6\text{H}_4\text{CONHC}_6\text{H}_4-\text{Y}$ ) in pyridine- $d_5$  and in dimethyl sulfoxide- $d_6$ . Normal substituent effects were reported for all nuclei, except for reversed correlation of the carbonyl carbon in the case where X is varied. For the series similar to benzanilides **1** (X = H, Y = *m*- and *p*-substituents)  $\rho$  values of 0.462 ppm ( $r = 0.981$ ) and 0.858 ppm ( $r = 0.970$ ) were reported for  $^1\text{H}$  and  $^{13}\text{C}(=\text{O})$ , respectively, in dimethyl sulfoxide- $d_6$  [7]. The authors then extended the study with fourteen *m*- and *p*-substituted benzanilides and reported  $\rho$  values of 0.459 ppm ( $r = 0.976$ ) and 0.853 ppm ( $r = 0.975$ ) [8]. They, however, used  $\sigma^-$  for the correlation of proton and  $\sigma$  for the correlation of

the carbonyl carbon. The  $\sigma$  and  $\sigma^-$  values are essentially identical for the substituents employed in the current investigation, except for the *p*-nitro ( $\text{NO}_2$ ) group whose  $\sigma$  and  $\sigma^-$  values are 0.78 and 1.24, respectively. Our data do not show significant improvement in correlation coefficient when  $\sigma^-$  was used. Therefore, we used  $\sigma$  for all correlations. Our results with **1** (X = H), which show  $\rho$  values of 0.640 ppm ( $r = 0.967$ ) for  $^1\text{H}$  and 0.953 ppm ( $r = 0.979$ ) for  $^{13}\text{C}(=\text{O})$ , are in reasonable agreement with the reported values. Small discrepancies might be due to the differences in concentration: about 100 mg in 0.6 ml (0.5-0.8 M) of solvent vs. 0.1 M in our measurement.

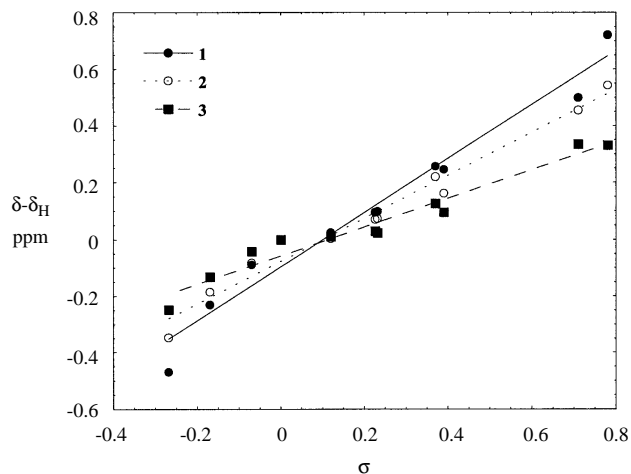
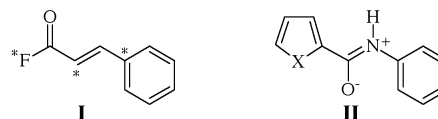
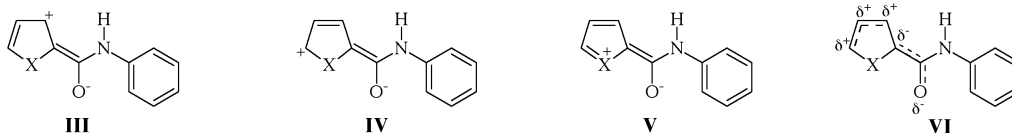


Figure 2. Correlation between  $\sigma$  and  $^{13}\text{C}$  chemical shifts of carbonyl carbon in **1-3** in dimethyl sulfoxide- $d_6$ .

The anilides may be considered structural analogs of cinnamoyl compounds **I** due to the resonance structure like **II**.



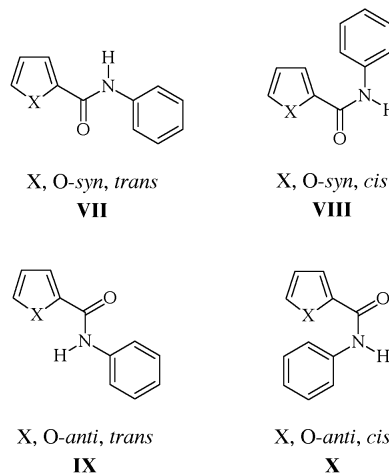


The normal (starred) and reverse (un-starred)  $^{13}\text{C}$  substituent chemical shift was observed in such a system [12]. Such rationale may explain the normal and reverse correlations of the carbonyl and *ipso*-carbons of **II**, respectively. However, the normal correlation of  $^{15}\text{N}$  of the benzamide series [7,8] is opposite to what would be expected by such analogy.

Apparently, the conjugation like **II** seems to compete with those of **III-V**. The overall effect may be a  $\pi$  polarization like **VI**. The induced charge should reflect the normal and reverse correlation of the substituent chemical shift.

There are several interesting observations in the correlation of the chemical shift values with the Hammett  $\sigma$ . First of all, the magnitude of the  $\rho$  value of each proton and carbon of **1** is the smallest among **1-3** except for the carbonyl carbon. This may be evidence that the benzene ring is purely aromatic, where the  $\pi$  electrons are completely delocalized while thiophene and furan rings are more like a system of conjugated double bonds. In other words, contribution of the resonance structures like **III-V** are not as significant in **1** as in **2** and **3**.

The magnitude of the  $\rho$  value of the *ortho*-H of **3** is about three times of that of **1**. Similarly, comparison of the *ortho*-H of **2** with that of **1** shows only twice the magnitude. The ratio of  $\rho_{o\text{-H}}/\rho_{p\text{-H}}$  are also quite contrasting; that is, the *para*-H is more sensitive to the substituent effect than *ortho*-H in **1** and **2**, whereas the opposite is the case with **3**.



**2**, X = S; **3**, X = O

On the other hand, the magnitude of the  $\rho$  value of the *ortho*-C of both **2** and **3** are about five times that of **1**. Furthermore,  $\rho_{o\text{-C}}/\rho_{p\text{-C}}$  is 0.38 of **1** indicating that the *para*-C is much more sensitive to the effect of the substituent than the *ortho*-C.

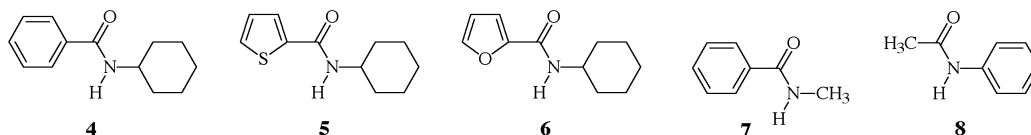
As shown in Table 2, there are two distinctive N-H signals appearing at around  $\delta$  10.3 and  $\delta$  3.3 for **1** and **3**. Integration of the two peaks typically show about 0.95 H and 0.05 H, respectively. Only **2a** shows such distinctive

Table 6

$^1\text{H}$  and  $^{13}\text{C}$  Chemical Shift Values of Substituted *N*-Cyclohexyl Amides **4-6**, *N*-methylbenzamide (**7**), and acetanilide (**8**) in Dimethyl Sulfoxide- $d_6$  (0.1 M)

	N-H	<i>o</i> -H	<i>m</i> -H	<i>p</i> -H	1'-H	2' <i>a</i> -H	2' <i>b</i> -H	3' <i>a</i> -H	3' <i>b</i> -H	4' <i>a</i> -H	4' <i>b</i> -H
<b>4</b>	8.19	7.83	7.44	7.50	3.76	1.81	1.31	1.73	1.31	1.61	1.13
<b>5</b>	8.20	7.78	7.12	7.71	3.70	1.81	1.29	1.73	1.29	1.60	1.12
<b>6</b>	8.07	7.08	6.60	7.79	3.70	1.76	1.29	1.71	1.29	1.59	1.11
<b>7</b>	8.42	7.83	7.45	7.51	3.34 [a]						
<b>8</b>	9.91	2.04 [a]				7.57		7.28		7.02	
	C=O	<i>i</i> -C	<i>o</i> -C	<i>m</i> -C	<i>p</i> -C	1'-C	2'-C	3'-C	4'-C		
<b>4</b>	165.80	135.38	127.72	128.58	131.36	48.79	25.43	32.89	25.75		
<b>5</b>	160.59	141.00	128.24	127.77	130.93	48.78	25.43	32.98	25.72		
<b>6</b>	157.28	148.61	113.52	112.18	145.14	48.14	25.42	32.85	25.66		
<b>7</b>	167.05	135.00	127.49	128.74	131.47	26.71 [a]					
<b>8</b>	168.73	24.48 [a]				139.81	119.44	129.13	123.43		

[a]  $\text{CH}_3$ .



signals among the thiophene series **2**. Integration of the peak at  $\delta$  10.3 of **2a-k**, however, shows a range of 0.91-0.97 H. This may be due to the overlapping of the second N-H signal in **2** with that of a small amount of water present in the solvent.

Correlation of the amidic N-H protons, which appear at around  $\delta$  10.3, with the Hammett  $\sigma$  show the largest slopes among the protons in each series. The slopes are 255.91 Hz (0.64 ppm), 240.08 Hz (0.60 ppm), and 265.37 Hz (0.66 ppm) for **1**, **2**, and **3**, respectively. The close  $\rho$  values with very close correlation coefficients ( $r = 0.962$ - $0.967$ )

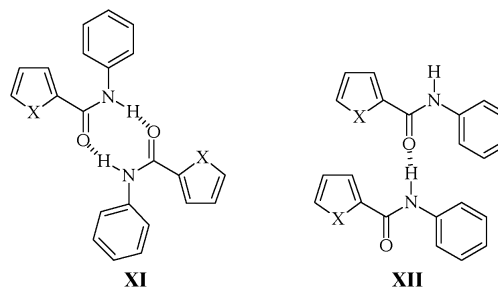


Table 7

Yields, Mp, and Elemental Analysis Data of Compounds 1-6

Compound	Yield %	Mp °C	Calcd				Observed			
			C, %	H, %	N, %	X, %	C, %	H, %	N, %	X, %
<b>1a</b>	70	157-158	64.46	4.16	11.56		64.18	4.35	11.66	
<b>1b</b>	40	136-137	56.55	3.65	5.07	28.94 [a]	56.32	3.72	5.29	28.76 [a]
<b>1c</b>	45	121-122	67.40	4.35	6.05	15.30 [b]	67.15	4.42	6.30	15.11 [b]
<b>1d</b>	77	109	73.99	5.77	6.16		73.77	5.84	6.35	
<b>1e</b>	67	119-120	79.59	6.20	6.63		78.87	5.81	7.35	
<b>1f</b>	57	198-199	64.46	4.16	11.56		64.25	4.30	11.73	
<b>1g</b>	27	203-204	56.55	3.65	5.07	28.94 [a]	56.28	3.59	4.95	28.65 [a]
<b>1h</b>	51	192-193	67.40	4.35	6.05	15.30 [b]	67.28	4.53	6.27	15.28 [b]
<b>1i</b>	67	157-158	73.99	5.77	6.16		73.78	5.95	6.35	
<b>1j</b>	48	158-159	79.59	6.20	6.63		79.38	6.45	6.66	
<b>1k</b>	57	163-165	79.17	5.62	7.10		78.87	5.81	7.35	
<b>2a</b>	43	143-144	53.22	3.25	11.28	12.91 [c]	53.01	3.35	11.28	12.69 [c]
<b>2b</b>	31	151	46.82	2.86	4.96	11.36 [c]	46.78	2.59	5.11	11.20 [c]
<b>2c</b>	36	191-191	55.58	3.39	5.89	13.49 [c]	55.39	3.48	6.10	13.28 [c]
<b>2d</b>	33	164-165	61.78	4.75	6.00	13.74 [c]	61.55	4.90	6.28	13.69 [c]
<b>2e</b>	72	146	66.33	5.10	6.45	14.75 [c]	66.15	5.06	6.70	14.59 [c]
<b>2f</b>	63	158-160	53.22	3.25	11.28	12.91 [c]	53.00	3.45	11.53	12.88 [c]
<b>2g</b>	71	218-219	46.82	2.86	4.96	11.36 [c]	46.59	2.78	5.03	11.21 [c]
<b>2h</b>	66	142-143	55.58	3.39	5.89	13.49 [c]	55.32	3.45	5.80	13.23 [c]
<b>2i</b>	74	137-140	61.78	4.75	6.00	13.74 [c]	61.49	4.90	6.21	13.55 [c]
<b>2j</b>	91	104-105	66.33	5.10	6.45	14.75 [c]	66.09	5.15	6.62	14.53 [c]
<b>2k</b>	85	172-173	60.26	4.14	6.39	14.62 [c]	60.01	4.22	6.52	14.38 [c]
<b>3a</b>	53	136	56.90	3.47	12.06		56.77	3.52	12.31	
<b>3b</b>	48	124-125	49.65	3.03	5.26	30.03 [a]	49.48	3.22	5.51	29.90 [a]
<b>3c</b>	41	117-118	59.61	3.64	6.32	15.99 [b]	59.43	3.75	6.55	15.78 [b]
<b>3d</b>	52	80-81	66.35	5.10	6.45		66.14	5.20	6.56	
<b>3e</b>	75	82-83	71.63	5.51	6.96		71.44	5.64	6.99	
<b>3f</b>	50	209-210	56.90	3.47	12.06		56.62	3.28	11.95	
<b>3g</b>	77	152-154	49.65	3.03	5.26	30.03 [a]	49.48	3.22	5.35	29.87 [a]
<b>3h</b>	51	151-152	59.61	3.64	6.32	15.99 [b]	59.58	3.72	6.52	15.75 [b]
<b>3i</b>	47	105	66.35	5.10	6.45		66.25	5.21	6.58	
<b>3j</b>	39	109-110	71.63	5.51	6.96		71.53	5.48	7.08	
<b>3k</b>	63	123-124	70.58	4.85	7.48		70.39	4.88	7.60	
<b>4</b>	89	152-153	76.81	8.43	6.89		76.59	8.48	6.75	
<b>5</b>	64	161	63.12	7.22	6.69	15.32 [c]	63.28	7.25	6.41	15.24 [c]
<b>6</b>	60	110-111	68.37	7.82	7.25		68.46	7.72	7.46	

[a] Bromine; [b] Chlorine; [c] Sulfur.

indicate that the chemical shift of N-H is solely influenced by the electronic effect of *m*- and *p*-substituted phenyl ring. On the other hand, the chemical shifts of other amidic signals in **1** and **3** are essentially  $\delta$  3.32  $\pm$  0.02 and they showed no correlation.

The two N-H signals are the result of rotamers such as **VII** and **VIII**. It is also conceivable that conformations such as **IX** and **X** may cause the appearance of the two N-H signals. However, it has been known that the conformation like **VII** is the most favorable energetically [13].

The presence of such rotamers was confirmed by the  $^{13}\text{C}$  nmr spectra, as listed in Table 3. Not only the carbonyl carbon, but also the *ipso*-C of the aroyl ring and the *ipso*- and *ortho*-C's in the anilino ring show distinctive peaks corresponding the minor rotamers.

The rotational barrier of the C-N bond of an amide is about 12-25 kcal/mole [14]. For monosubstituted acetanilide, the more stable conformer is the one with phenyl group *cis* to the carbonyl oxygen [15]. In order to examine the nature of the two distinctive N-H signals in **1-3** we prepared *N*-cyclohexylbenzamide (**4**), *N*-cyclohexyl-2-thienamide (**5**), and *N*-cyclohexyl-2-furamide (**6**) and obtained their nmr spectra in 0.1 *M* solutions of dimethyl sulfoxide- $d_6$ . For the purpose of comparison, the nmr spectra of *N*-methylbenzamide (**7**) and acetanilide (**8**) were also obtained at 0.1 *M* dimethyl sulfoxide- $d_6$  and the resulting values are listed in Table 6.

There was no signal corresponding to different rotamers of **4-8** in either  $^1\text{H}$  or  $^{13}\text{C}$  nmr spectra. Replacement of the phenyl group with a cyclohexyl group causes upfield shift of the protons in the aroyl ring by 0.09-0.13 ppm in **4** and 0.10-0.26 ppm in **5** and **6**. Usually *ortho*-H's are affected most. More importantly, the N-H signals appear at  $\delta$  8.00-8.20 as doublets with coupling constant of *ca.* 8 Hz. This means that the replacement causes the N-H signal shift to upfield by more than 2 ppm. The N-H signal of acetanilide (**8**) appears at  $\delta$  9.91 as a sharp singlet whereas it appears at  $\delta$  8.42 as a broad singlet in the case of *N*-methylbenzamide (**7**). The methyl signal appears as a doublet at  $\delta$  2.79 with a coupling constant of 4.6 Hz.

The chemical shift of N-H in rotamer **VIII** seems to be much more influenced by the concentration than that of **VII** as shown in Table 1. As the concentration increases, the amide group may form intermolecular hydrogen bonding like in **XI**, which causes the down field shift. Such dimerization is not feasible in rotamer **VII**. The intermolecular hydrogen bonding like in **XII** may be possible with the rotamer **VII**. Such hydrogen bonding should affect the chemical shift of N-H and *ortho*-H because they are closer to the electronic influence of the

amide group than *meta*- and *para*-Hs. Much larger values of the slopes of N-H, *ortho*-H and *para*-H in Table 1 are consistent with such rationale.

In conclusion, the nmr spectra of anilides of benzoic acid, 2-thienoic acid, and 2-furoic acid show good correlation with the Hammett  $\sigma$ . The plot of the chemical shift values of the 2-thienanilides or 2-furanilides against those of the benzanilides provides relative magnitude of aromaticity indices. Values of 0.79 and 0.52 were obtained for thiophene and furan, respectively.

## EXPERIMENTAL

Melting points were determined on a Fischer MEL-TEMP apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Bruker DPX-400 FT NMR spectrometer in the Central Lab of Kangwon National University at 400 MHz for  $^1\text{H}$  and 100 MHz for  $^{13}\text{C}$  and were referenced to tetramethylsilane. The concentration of the solution was 0.10 *M* in dimethyl sulfoxide- $d_6$  and chloroform-*d*. The Central Lab of Kangwon National University performed elemental analyses.

### An Illustrative Procedure for Preparation of *m*- and *p*-Substituted Anilides **1-3**.

A mixture of a carboxylic acid (8 mmoles) and thionyl chloride (28 mmoles) was heated at reflux for 30 minutes. The resulting solution was evaporated under aspirator pressure to remove excess thionyl chloride. The residual liquid was cooled in an ice-water bath and a solution of substituted aniline (16 mmoles) and triethylamine (10 mmoles) in dichloromethane (15 ml) was added slowly. The solution was heated at reflux for 1 hour. It was then treated with saturated sodium bicarbonate solution until the aqueous layer was slightly basic (pH  $\sim$ 8). The organic layer was washed with water (10 ml) and dried over anhydrous sodium sulfate. The solvent was removed and the resulting solid was recrystallized from ethanol. The yields, mp, and elemental analyses data are listed in Table 7.

### An Illustrative Procedure for Preparation of *N*-Cyclohexyl Amides **4-6**.

A solution of cyclohexylamine (4 mmoles) and triethylamine (4 mmoles) in dichloromethane (10 ml) was added drop-wise to an ice-cold solution of acyl chloride (3 mmoles) in dichloromethane (10 ml). The resulting solution was heated at reflux for 1 hour. The solution was partitioned in dichloromethane (30 ml) and water (50 ml). The organic layer was separated, dried over sodium sulfate, and evaporated. The residue was recrystallized from ethanol. The yields, mp, and elemental analysis data are listed in Table 7.

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