Bull. Chem. Soc. Jpn., 58, 2832—2839 (1985) [Vol. 58, No. 10

The Carbon-13 NMR Spectra and Electronic Structure of 3*H*-Phenoxazin-3-ones

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(Received March 27, 1985)

The ^{13}C NMR chemical shifts of 3*H*-phenoxazin-3-one (**1**) and eighteen of its derivatives are reported. The chemical shifts of **1** can be explained in terms of a successive polarization of the π-conjugated framework by an electron-withdrawing carbonyl group and a π-donating ether oxygen. The principal factor solution for the chemical shifts of the 2-substituted 3*H*-phenoxazin-3-ones suggests that the first and the second factors collectively controlling the 2-substituent effect are electronic and steric effects, respectively. A dual substituent parameter analysis elucidated the transmission modes of the polar and resonance effects of the 2-substituents, and that the first and the fourth factor loadings multiplied by the corresponding standard deviation of the chemical shifts correlate with the CNDO/2 substituent-induced σ and π charge densities.

Phenoxazin-3-ones and their imine analogues are the chromophores in a number of synthetic dyestuffs such as oxazine dyes and redox indicators.[1] As is well known, 3*H*-phenoxazin-3-one (**1**) is the chromophore part of the actinomycins produced by a Streptomyces species of soil bacteria and the initial step of the bonding between actinomycin D and DNA to inhibit RNA synthesis is considered to be the intercalation of a phenoxazin-3-one ring system between the guanine-cytosine base pairs.[2]

There have been few investigations of the electronic properties of 3*H*-phenoxazin-3-ones,[3] although many papers have been devoted to their syntheses and analyses of their IR,[4,5] UV,[4] and ^{1}H NMR spectra[6] in connection with advanced dye and medical chemistry. Pashkevich *et al.* have studied the annelation effect of a benzene ring on the electronic structure of all possible mono- and diannelated derivatives of **1** by means of the Hückel MO method and found a satisfactory correlation between the experimental and calculated energies of the $\pi\rightarrow\pi^*$ transitions.[3]

^{13}C NMR is a very powerful analytical tool to study the electronic structure of a carbon skeleton and the nature of bonding. In a previous paper, we reported the ^{13}C NMR chemical shifts of 3*H*-phenothiazin-3-one and eleven of its methyl derivatives.[7] In this paper, we extend the ^{13}C NMR chemical shifts of **1** and its derivatives, including the 2-substituents, and elucidate the transmission pattern of an electronic substituent effect by means of both Taft's dual substituent parameter (DSP) treatment[8] and the principal factor method.[9]

Experimental

Materials. The syntheses of **1**[10] and its 2-amino- (**4**),[10] 2-acetamido- (**7**),[10] 2-anilino- (**8**),[11] 2-hydroxy- (**10**),[12] 7-methoxy- (**13**),[13] 7-ethoxy- (**14**),[14] 7-acetoxy- (**15**),[14] 2-amino-1,9-dimethyl- (**18**),[5] and 2-amino-4,6-dimethyl- (**19**)[5] derivatives were performed according to the usual methods. 2-Methyl- (**2**),[15] 2-ethyl- (**3**),[15] 2-methylamino- (**5**),[16] 2-ethylamino-(**6**),[16] 2-(*N*-methylanilino)- (**9**),[17] 4-methyl- (**11**),[15] 2,4-dimethyl- (**16**),[15] and 2,4-diethyl-3*H*-phenoxazin-3-ones (**17**)[15] were prepared as described in previous papers. *N*-Phenyl-*p*-benzoquinone monoimine (**20**) was prepared according to the method of Uemura and Abe.[18] All the compounds were purified by TLC and column chromatography and checked by means of their IR and ^{1}H NMR spectra. Their spectral and physical properties were in agreement with available data from the literature. 4-Ethyl-3*H*-phenoxazin-3-one (**12**) was synthesized as in the case of **11**; mp 150—151 °C. Anal. Found: C, 74.42; H, 4.78; N, 5.91%. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%.

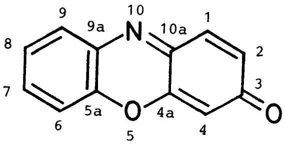


Fig. 1. Numbering of **1**.

Procedures. The ^{13}C NMR spectra were recorded on a Varian XL-200 Fourier-transform spectrometer at room temperature at 50.3 MHz using 10-mm sample tubes and a deuterium lock. Samples were prepared in a $CDCl_3$ solvent with tetramethylsilane as an internal reference except for **10** in dimethyl-d_6 sulfoxide. In the case of the dimethyl sulfoxide solvent, the ^{13}C NMR data were converted on the basis of 39.5 ppm of the dimethyl sulfoxide reference peak. A linear least-squares analysis for Taft's DSP equation was carried out by means of the Gauss-Newton method. The values of substituent constants, such as σ_I, $\sigma_R{}^0$, $\sigma_R{}^{BA}$, $\sigma_R{}^+$, F, and R for the electronic effect on the 2-substituents, were taken from Refs. 8c and 19. The values of the substituent constants not found in the literature were estimated from the known values of the corresponding σ_m, $\sigma_p{}^{BA}$, $\sigma_p{}^+$, and $\sigma_p{}^0$ by using the equations $\sigma_I=1.5\sigma_m-0.5\sigma_p$ and $\sigma_R{}^A=\sigma_p{}^A-\sigma_I$ where suffix A stands for 0, BA or +. The values of the Inamoto-Masuda group electronegativity χ and the inductive scale ι not found in Ref. 20 are as follows: $NHCH_3$, 3.031, 2.496; NHC_2H_5, 3.032, 2.496; NHC_6H_5, 3.034, 2.498; $NCH_3C_6H_5$, 3.016, 2.486.[21] Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected.

Theoretical

CNDO/2 calculations[22] were carried out as in a previous paper.[7] The planar geometry of **1** was determined from the X-ray data[2] of actinomycin D obtained by means of a light-atom analysis and transferred to its

TABLE 1. ^{13}C NMR CHEMICAL SHIFTS OF 3*H*-PHENOXAZIN-3-ONES[a]

Substituent	Chemical shift, δ												
	C-1	C-2	C-3	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a	Others
Nil(**1**)	135.2	134.8	186.4	107.0	149.7	148.8	116.2	132.8	125.5	130.5	133.4	144.0	
2-Me(**2**)	132.1	[144.4]	186.2	106.5	149.3	149.0	116.1	131.3	125.3	130.1	133.5	143.8	16.5(Me)
2-Et(**3**)	130.1	[149.6]	185.9	106.7	149.2	149.1	116.1	132.0	125.2	129.7	133.5	143.8	22.6(CH$_2$), 12.2(Me)
2-NH$_2$(**4**)	100.9	[151.0]	178.9	104.2	148.7	146.0	116.1	129.6	125.3	128.8	133.7	142.8	
2-NHMe(**5**)	96.1	[150.0]	180.3	103.9	148.5	146.8	116.0	128.9	125.3	128.4	134.1	142.6	29.3(Me)
2-NHEt(**6**)	96.1	[149.9]	180.3	103.9	148.5	145.7	115.9	128.8	125.2	128.4	134.1	142.6	37.4(CH$_2$), 13.7(Me)
2-NHAc(**7**)	113.9	[149.4]	179.7	104.1	149.1	147.9	116.1	131.8	125.7	130.1	134.0	143.3	24.9(Me), 169.2(CO)
2-NHPh(**8**)	112.7	[149.8]	180.3	104.0	148.7	146.5	116.1	129.7	125.5	128.8	134.2	142.8	146.5(C_j), 121.6(C_o), 129.6(C_m), 124.6(C_p)
2-NMePh(**9**)	110.0	[149.3]	181.7	106.5	148.9	148.6	116.0	129.8	125.1	128.8	133.9	142.8	148.5(C_j), 124.3(C_o), 129.4(C_m), 125.4(C_p), 42.8(Me)
2-OH(**10**)	103.1	[155.6]	185.1	104.0	149.2	147.3	115.7	127.0	125.0	126.8	134.1	141.5	
4-Me(**11**)	134.7	134.0	185.9	[116.7]	145.8	148.5	116.1	132.4	125.1	130.2	133.3	143.8	9.7(Me)
4-Et(**12**)	134.9	134.0	185.3	[121.4]	145.3	149.5	116.1	132.2	125.1	130.2	133.4	144.5	15.7(CH$_2$), 12.7(Me)
7-OMe(**13**)	134.7	134.2	186.3	106.7	149.9	148.2	100.1	[163.7]	113.7	131.6	128.4	145.6	56.2(Me)
7-OEt(**14**)	134.7	134.2	186.4	106.7	149.9	145.7[b]	100.5	[163.1]	114.0	131.6	128.3	145.5[b]	64.7(CH$_2$), 14.6(Me)
7-OAc(**15**)	135.2	134.8	186.3	107.3	149.3	148.4	109.7	[153.5]	119.2	131.2	131.3	144.4	21.1(Me), 168.5(CO)
2,4-Me$_2$(**16**)	131.6	[143.6][b]	185.8	[115.0]	145.5	149.0	116.0	130.6	124.9	129.9	133.3	144.3[b]	16.8(2-Me), 7.8(4-Me)
2,4-Et$_2$(**17**)	129.8	[149.0]	185.0	[120.9]	145.0[b]	149.4	116.0	131.5	124.9	129.0	133.4	144.4[b]	22.9(2-CH$_2$), 16.0(4-CH$_2$), 12.8(4-Me), 12.1(2-Me)
2-NH$_2$-1,9-Me$_2$(**18**)	[113.4]	[143.2]	180.1	102.8	149.4	142.8[b]	113.4	129.0	125.9	[138.3]	132.3	142.6[b]	9.5(1-Me), 16.8(9-Me)
2-NH$_2$-4,6-Me$_2$(**19**)	100.2	[148.3]	177.9	[114.9]	145.2	147.9	[125.4]	130.7	124.3	126.4	134.3	142.7	14.9(6-Me), 7.7(4-Me)
N-Ph-*p*-QI(**20**)[c]	141.7	132.7	187.3	128.0	133.4	120.5	129.0	126.1	129.0	120.5	149.4	157.2	
Δδ(PXZ—PTZ)[d]	−4.7	−0.1	3.8	−12.6	13.9	25.0	−8.9	1.5	−2.7	−3.5	−5.7	−2.1	

a) Square brackets denote the positions of substituted carbons. b) Similar values may be interchanged. c) *N*-Phenyl-*p*-benzoquinone monoimine numbered as for **1**. d) Chemical shift difference between **1** and 3*H*-phenothiazin-3-one.

derivatives. The atomic coordinates of substituents were computed from known data regarding the corresponding bond lengths and bond angles.[23] The CNDO/2 calculations of **4** shows that the pyramidal structure of an amino group, where one of the NH bonds is coplanar with the quinonoid ring and turns toward the CO group, is more stable than the planar structure. Therefore, CNDO/2 calculations of the 2-amino derivatives were carried out for the pyramidal structure. The geometry of *N*-phenyl-*p*-benzoquinone monoimine was estimated using the data of *N*-chloro-*p*-benzoquinone monoimine described in a preceding paper[7] and assuming a torsional angle of 30° between the phenyl and quinonoid rings.

Results and Discussion

*^{13}C Chemical Shifts of 3*H*-Phenoxazin-3-one.* The ^{13}C chemical shifts of 3*H*-phenoxazin-3-ones are listed in Table 1. Their chemical shifts can be assigned on the basis of those of 3*H*-phenothiazin-3-ones[7] and phenyl vinyl ether,[24] and the estimation from the substituent-induced chemical shifts (SCS) of the corresponding group on benzenes and olefins.[25] The replacement of the bridged S atom of 3*H*-phenothiazin-3-one by an O atom resulted in downfield shifts of C-3, C-4a, C-5a, and C-7, and upfield shifts of the other carbons, *i.e.*, a symmetrical change in the sign of the SCS toward the N–O axis.

The signal at δ 186.4 for the carbonyl carbon of **1** appeared at a lower field (by 3.8 ppm) than that of 3*H*-phenothiazin-3-one, but higher (by 0.9 ppm) than that of **20**. A similar result has been observed regarding the difference (4.2 ppm) of the chemical shifts of the carbonyl carbons between 3-ethylthio-5,6-dimethyl- and 3-ethoxy-2-cyclohexenones.[19b] The remarkably high shielding of C-4 of **1** suggests a resonance of the vinyl ether type, *i.e.*, a strong π-polarization of the olefinic double bond by the ether oxygen. The high shielding of C-6 and C-8 is ascribed to the increased $2p_\pi$ electron densities because of the ortho and para positions with respect to the ether oxygen. The values of the upfield shifts of C-4, C-6, C-8, and C-9a caused by the oxygen substitution of 3*H*-phenothiazin-3-one were lower than those of the corresponding carbons between the phenyl vinyl ether and the phenyl vinyl sulfide.[24] From the chemical shifts of C-1, C-3, and C-9, the partial positive charge of the carbonyl carbon of **1** seems to be less delocalized than that of the 3*H*-phenothiazin-3-one.

It is considered that **20** may serve as a reference compound to elucidate the relative abilities of O and S atoms interposed between two conjugated rings to transmit electronic effects. However, the finding that the ^{13}C chemical shifts of **20** are similar to those of the corresponding carbons of aniline[25] and *N*-chloro-*p*-benzoquinone monoimine[7] suggests a remarkably twisted structure between the phenyl and the quinonoid rings of **20** owing to a steric hindrance. Therefore, it is reasonable that the introduction of the bridged oxygen on **20** resulted in an SCS similar to or a little more than those of vinyl ether toward benzene

TABLE 2. THE FACTOR SCORES OF THE 2-SUBSTITUENTS OBTAINED BY THE PRINCIPAL FACTOR METHOD

Substituent	F_I	F_{II}	F_{III}	F_{IV}
H	1.830	−0.087	0.345	−2.063
Me	1.176	−0.619	−0.496	0.236
Et	1.032	−0.726	−0.478	1.495
NH_2	−0.546	0.694	−1.207	−0.396
NHMe	−0.880	0.431	−0.509	−0.030
NHEt	−1.050	0.386	−0.993	−0.824
NHAc	0.297	1.664	1.873	0.965
NHPh	−0.455	0.953	0.530	−0.117
NMePh	−0.089	−0.654	−0.643	1.206
OH	−1.314	−2.040	1.581	−0.468

for the ortho and the ipso carbons but the remarkable downfield shift for the meta carbon. C-10a moves to a higher field by 13.2 ppm relative to the imino carbon of **20**; the considerable upfield shift may be explained in terms of the nature of the oxazine ring rather than the substituent effect on the quinone imine.

Substituent Effect. To evaluate the factors controlling the chemical shifts of all the carbons of the 2-substituted phenoxazin-3-ones and their contributions, data analyses of the chemical shifts of **1—10** were performed using the principal factor method.[9] In the factor analysis, the chemical shift (or SCS) data matrix was transformed into a standard score matrix composed of 10×12 elements using Eq. 1:

$$z_{ij} = (\delta_{ij}-\bar{\delta}_j)/\sigma_j \tag{1}$$

where z_{ij} and δ_{ij} are the elements of the standard score matrix and the original chemical shift (or SCS) data matrix for the carbon j on substituent i, respectively; $\bar{\delta}_j$ and σ_j are mean and the standard deviations of variable j, respectively. The factor-loading and score matrices were derived from the correlation matrix, between the variables, whose diagonal elements are equal to communality by maximizing the sum of the squared loadings of the first factor (F_I). Thus,

$$z_{ij} = \sum_{m=1}^{M} f_{im}a_{jm} \tag{2}$$

where a_{jm} is the m th factor loading for variable j and f_{im} the m th factor score for substituent i, equivalent to the substituent constant. M indicates the upper limit of m and is equal to the number of positive eigenvalues obtained by the diagonalization of the correlation matrix, 11 in this case. From Eqs. 1 and 2

$$\delta_{ij} = \sum_{m=1}^{M} f_{im}a_{jm}\sigma_j + \bar{\delta}_j. \tag{3}$$

Table 2 shows the factor scores of the 2-substituents of 3*H*-phenoxazin-3-ones calculated by the principal-factor method. None of the factor score series obtained were found to be parallel to a single known substituent parameter. From the correlation of the factor scores with various substituent scales, the following multiparameter equations were found to be statistically sufficient to interpret F_I—F_{IV}.[26]

$$F_I = -2.55\Delta\iota + 0.67\sigma_R^+ + 1.76 \quad (r=0.985,\ n=7) \tag{4}$$

$$F_{II} = -21.89(C_2\text{–}X) + 23.25B_3 - 4.65B_3^2 + 4.89 \quad (r=0.967,\ n=8) \tag{5}$$

$$F_{III} = 12.24\sigma_I + 5.95\sigma_R^0 + 0.36B_4' - 0.17 \quad (r=0.975,\ n=7) \tag{6}$$

$$F_{IV}{}^{27)} = 29.27\Delta\iota + 3.92\sigma_R^+ - 0.79B_2 - 4.91N - 1.30 \quad (r=0.973,\ n=7) \tag{7}$$

where C_2–X represents the atomic distance[23] between C-2 and the substituent X, and B_2, B_3, and B_4' stand for the STERIMOL parameters[28] of the substituent. B_4' cooperates with B_1 as the wide scale of the substituent and corresponds to B_4 except for B_2 in the cases of the NH_2 and $NHCOCH_3$ groups. N in Eq. 7 denotes the number of lone-pair electrons of the central atom of substituent X.

As Eqs. 4 and 5 suggest, the F_I and F_{II} terms are associated with the electronic and the steric effects of the substituents, respectively. The F_{III} and the F_{IV} scales seem to depend not only on the electronic effect, but also on the steric effect, provided that F_{IV} can also be explained mainly in terms of the STERIMOL B_2 parameter as well as the electronic substituent parameter.[27]

Table 3 lists the factor loadings of the carbons along with the average and standard-deviation values of the chemical shifts. The above four factors account for 96% of the variability in the chemical-shift data matrix. The chemical shifts for C-1 induced by the 2-substituents can be explained mainly in terms of the first factor, *i.e.*, only the electronic parameter. As the contribution of the first factor (for the chemical shifts of all the carbons of the 2-substituted 3*H*-phenoxazin-3-ones) is only 67.4%, two or three factors including the steric factors are, in general, necessary to accurately evaluate the substituent effects that affect the chemical shifts for the other carbons; in particular, for the SCS of C-2, F_I and F_{IV} are taken into consideration.

As the product of the factor loading and the standard deviation of the chemical shifts shows, the first factor has a maximum effect on the chemical shift of C-1 and its electronic variation is transmitted to the alternative carbons (C-3, and C-9, C-5a, and C-7) which are the benzenoid ortho and para carbons relative to the N atom. The attenuation factors are 13, 7, 7, and 12%, respectively. Although F_I, F_{III}, and F_{IV} are associated with the resonance effect of the 2-substituents, the sign of the factor loading of the first factor coincides with that of the corresponding transmission coefficient of the resonance effect in Taft's DSP treatment because of

TABLE 3. THE FACTOR LOADINGS OF 2-SUBSTITUTED 3H-PHENOXAZIN-3-ONES OBTAINED BY THE PRINCIPAL FACTOR METHOD[a)]

Position	Factor loading				Main factor[b)]	$\bar{\delta}$[c)]	$\overline{\mathrm{SCS}}$[d)]	S.D.[e)]	I×S.D.	II×S.D.
	I	II	III	IV						
C-1	0.951	−0.178	0.127	0.038	I	113.02	−22.21	14.05	13.36	−2.50
C-2	−0.822	−0.122	0.093	0.482	I, IV	148.37	13.59	5.20	−4.27	−0.63
C-3	0.623	−0.727	0.131	−0.119	I, II	182.47	−3.88	2.86	1.78	−2.08
C-4	0.843	−0.407	−0.224	0.117	I, II	105.06	−1.90	1.30	1.10	−0.53
C-4a	0.796	−0.391	0.389	−0.160	I, II, III	148.98	−0.73	0.37	0.29	−0.14
C-5a	0.801	−0.404	0.176	0.341	I, II, IV	147.58	−1.21	1.24	0.99	−0.50
C-6	0.812	0.558	−0.100	0.024	I, II	116.03	−0.16	0.12	0.10	0.07
C-7	0.939	0.303	0.018	0.099	I	130.18	−2.65	1.70	1.60	0.52
C-8	0.422	0.822	0.378	−0.014	I, II, III	125.31	−0.17	0.19	0.08	0.16
C-9	0.894	0.425	−0.047	0.072	I, II	129.05	−1.42	1.04	0.93	0.44
C-9a	−0.858	0.241	0.298	0.070	I	133.86	0.45	0.29	−0.25	0.07
C-10a	0.935	0.258	−0.198	0.086	I	142.98	−0.98	0.71	0.66	0.18
Factor contributions/%	67.4	20.4	4.7	3.6	2.1(V)[f)]	1.1(VI)[g)]				

a) Along with the product of the factor loading and the standard deviation of the ^{13}C chemical shifts. b) The contribution of the factor loading clearing the lower limit ($a_{ij}^2>0.10$) is important. c) The average of the chemical shift. d) The average of the SCS. e) The standard deviation of the chemical shift. f) The fifth factor contribution. g) The sixth factor contribution.

the high contribution (*vide infra*). In the factor loading of the second factor having a steric character, the sign for almost all the quinonoid carbons is opposite to that for most benzenoid carbons. It is reasonable that the second factor causes the relatively large changes in the chemical shifts of C-1 and C-3.

Plots of the chemical shifts of C-2 versus the Inamoto-Masuda group electronegativities χ of the 2-substituents (**1**, **4**—**10**) excluding alkyl group afforded the excellent correlation;

$$\delta = 16.25\chi + 100.37 \quad (r=0.985,\ n=8) \tag{8}$$

This finding reinforces such an explanation that the contributions of the $\sigma_R{}^+$ terms in F_I and F_{IV} mainly controlling the SCS of C-2 offset each other by multiplicating their factor loadings.[29)] The C_α or C_{ipso} SCS of monosubstituted methanes,[30,31)] ethanes,[30)] and benzenes[30,31)] have also been reported to be proportional to the group electronegativity of the substituent.

Taft's DSP analysis is convenient for a simple interpretation of substituent effects in terms of the relative proportions of field/inductive and resonance effects shown by Eq. 9.

$$\delta = \rho_I\sigma_I + \rho_R\sigma_R + \delta_0 \tag{9}$$

where δ and δ_0 indicate the ^{13}C chemical shift of the carbon of interest and the intercept of the DSP equation respectively. ρ_I and ρ_R represent the transmission coefficients of the field/inductive and the resonance effects, respectively.

Although the pairs of substituent parameters giving the best correlation with the chemical shifts depend on the positions of the carbons, the chemical shifts of C-1 correlate very well with all of the substituent constants used for the DSP equation. As Eq. 7 shows, the behavior of the alkyl groups for C-2 appears to be different from that of the other 2-substituents in terms of an orbital-repulsion effect due to the absence of lone-pair electrons. The ρ values were obtained by applying Eq. 9 to the chemical shifts of **1** and six 2-substituted analogues (**2**, **3**, **4**, **7**, **8**, and **10**).

The polar and resonance effects will be discussed on the basis of both the ρ_I—$\rho_R{}^0$ values which are well applied to other compounds and the ρ_I—$\rho_R{}^+$ values having generally high correlation coefficients for the quinonoid carbons. Table 4 shows the ρ values for all the carbons of 2-substituted 3*H*-phenoxazin-3-ones. The resonance effect of the 2-substituents is most strongly transmitted to C-1; the magnitude ($\rho_R{}^0=70.73$) for the resonance effect is similar to those ($\rho_R{}^0=63.03$ and 75.54 respectively) for the effects in 3-substituted 2-cyclohexenes[32)] and 2-substituted 1,4-naphthoquinoes.[33)] The resonance effect of C-1 is transmitted to the alternant carbons, C-3 and C-4a, with attenuation factors of 20—22% and 2—3%, respectively. The magnitude of the reverse resonance effect of C-2 is 46—53% as high as that for the normal resonance effect of C-1. Those attenuation ratios are somewhat high relative to the values estimated by the first factor because not only the first factor but also the third and the fourth factors contribute to the resonance effect. The $\rho_R{}^+$ values of the benzenoid meta carbons, C-6 and C-8, relative to the N atom are almost zero.

It is reasonable from the resonance of the α,β-unsaturated ketone or imine between C-4a and C-3 or N that the $\rho_R{}^+$ value of C-4a is positive; the presence of an enone resonance between C-3 and C-4a is supported by indications that the signs of factor loadings from F_I to F_{IV} for C-4a are equal to those for C-3.

There are several main factors such as classical σ-inductive, π-inductive, direct through-space field, and

TABLE 4. CORRELATIONS OF THE ^{13}C CHEMICAL SHIFTS OF 3*H*-PHENOXAZIN-3-ONES WITH SUBSTITUENT CONSTANTS[a)]

Symbol[b)]	C-1	C-2[c)]	C-3[d)]	C-4	C-4a	C-5a	C-6	C-7	C-8[d)]	C-9	C-9a	C-10a
ρ_I	−18.38	19.33	−11.63	−3.56	1.15	2.14	−0.29	−0.14	1.68	−0.38	1.13	−1.83
$\rho_R{}^0$	70.73	−32.44	14.44	5.42	2.11	7.53	0.40	9.31	0.59	5.11	−0.72	3.22
δ_0	136.12	136.40	186.43	106.74	149.53	149.38	116.18	132.77	125.44	130.49	133.52	144.01
r	0.993	0.940	0.966	0.921	0.858	0.904	0.659	0.813	0.899	0.737	0.749	0.854
f	0.120	0.341	0.260	0.390	0.514	0.427	0.752	0.582	0.437	0.676	0.663	0.520
ρ_I	−31.06	28.54	−12.44	−3.82	0.89	1.30	−0.42	−1.85	1.47	−1.51	0.95	−2.42
$\rho_R{}^+$	17.32	−9.17	3.87	1.58	0.56	2.02	0.08	2.16	0.09	1.18	−0.29	0.78
δ_0	134.82	134.91	186.37	106.79	149.52	149.35	116.16	132.53	125.40	130.35	133.46	143.94
r	0.989	0.980	0.998	0.975	0.916	0.965	0.620	0.786	0.829	0.710	0.832	0.851
f	0.147	0.200	0.068	0.224	0.402	0.262	0.784	0.619	0.560	0.704	0.555	0.526

a) Calculated from the seven point data set of the chemical shifts of **1**—**4**, **7**, **8**, and **10** except for C-2, C-3, and C-8. b) The symbols of ρ_I, $\rho_R{}^0$, and $\rho_R{}^+$ indicate the transmission coefficients having connections with σ_I, $\sigma_R{}^0$, and $\sigma_R{}^+$ respectively; δ_0 and r represent the intercept and the correlation coefficient for the DSP equation. f=S. D./R. M. S. c) Alkyl groups were excluded from the correlation. d) Calculated from the data with the hydroxyl group excluded.

TABLE 5. CNDO/2 π AND TOTAL ELECTRON DENSITIES OF 3*H*-PHENOXAZIN-3-ONES

Substituent	C-1	C-2	C-3	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-9a	C-10a
Nil(**1**)	3.9959	4.0454	3.7474	4.1354	3.8122	3.8332	4.0504	3.9692	4.0097	3.9943	3.9552	3.9348
	π 0.9800	1.0008	0.8578	1.1332	0.9263	0.9509	1.0569	0.9648	1.0306	0.9779	1.0468	1.0073
2-Me(**2**)	4.0249	3.9988	3.7540	4.1387	3.8117	3.8365	4.0494	3.9721	4.0087	3.9973	3.9529	3.9312
	π 1.0253	0.9632	0.8615	1.1372	0.9222	0.9558	1.0557	0.9697	1.0292	0.9823	1.0418	0.9969
2-Et(**3**)	4.0306	3.9991	3.7549	4.1389	3.8117	3.8372	4.0491	3.9727	4.0084	3.9979	3.9523	3.9296
	π 1.0349	0.9564	0.8624	1.1380	0.9215	0.9570	1.0553	0.9708	1.0288	0.9832	1.0407	0.9948
2-NH$_2$(**4**)	4.0659	3.9155	3.7671	4.1386	3.8115	3.8403	4.0480	3.9751	4.0072	4.0001	3.9501	3.9214
	π 1.0764	0.9398	0.8632	1.1434	0.9172	0.9620	1.0538	0.9749	1.0270	0.9870	1.0365	0.9871
2-NHMe(**5**)	4.0928	3.8879	3.7672	4.1396	3.8107	3.8443	4.0464	3.9786	4.0059	4.0041	3.9473	3.9131
	π 1.1225	0.9308	0.8656	1.1484	0.9123	0.9684	1.0519	0.9809	1.0252	0.9927	1.0308	0.9763
2-NHEt(**6**)	4.0723	3.9123	3.7684	4.1387	3.8117	3.8413	4.0477	3.9760	4.0069	4.0011	3.9493	3.9199
	π 1.0871	0.9287	0.8645	1.1441	0.9167	0.9635	1.0534	0.9764	1.0266	0.9884	1.0350	0.9843
2-OH(**10**)	4.0793	3.8553	3.7762	4.1376	3.8105	3.8400	4.0475	3.9743	4.0070	3.9995	3.9504	3.9185
	π 1.0915	0.9389	0.8645	1.1476	0.9140	0.9624	1.0535	0.9737	1.0266	0.9860	1.0375	0.9889
4-Me(**11**)	3.9955	4.0481	3.7557	4.0802	3.8392	3.8341	4.0508	3.9708	4.0096	3.9961	3.9534	3.9317
	π 0.9776	1.0039	0.8637	1.0957	0.9646	0.9516	1.0573	0.9673	1.0305	0.9803	1.0438	1.0001
4-Et(**12**)	3.9954	4.0478	3.7564	4.0798	3.8437	3.8340	4.0505	3.9709	4.0096	3.9970	3.9539	3.9296
	π 0.9770	1.0046	0.8645	1.0887	0.9734	0.9515	1.0572	0.9677	1.0306	0.9811	1.0438	0.9984
7-OMe(**13**)	3.9926	4.0512	3.7459	4.1378	3.8104	3.8111	4.1094	3.7848	4.0780	3.9707	3.9814	3.9468
	π 0.9760	1.0101	0.8550	1.1363	0.9264	0.9220	1.1219	0.9098	1.0971	0.9466	1.0883	1.0288
7-OEt(**14**)	3.9922	4.0521	3.7456	4.1390	3.8101	3.8107	4.1200	3.7860	4.0685	3.9707	3.9827	3.9483
	π 0.9753	1.0115	0.8544	1.1381	0.9257	0.9196	1.1288	0.9064	1.0919	0.9475	1.0904	1.0314
7-OAc(**15**)	3.9954	4.0400	3.7295	4.1273	3.8133	3.8177	4.0861	3.7858	4.0200	3.9802	3.9531	3.9242
	π 0.9830	0.9945	0.8824	1.1212	0.9357	0.9409	1.0910	1.0015	1.0478	0.9700	1.0418	0.9920
2,4-Me$_2$(**16**)	4.0244	4.0016	3.7624	4.0837	3.8384	3.8372	4.0498	3.9735	4.0086	3.9989	3.9512	3.9282
	π 1.0228	0.9665	0.8676	1.0999	0.9602	0.9563	1.0560	0.9719	1.0291	0.9845	1.0390	0.9902
2-NH$_2$-1,9-Me$_2$(**18**)	4.0192	3.9408	3.7670	4.1401	3.8130	3.8333	4.0595	3.9671	4.0279	3.9553	3.9702	3.9361
	π 1.0401	0.9800	0.8603	1.1438	0.9188	0.9479	1.0717	0.9585	1.0552	0.9513	1.0657	1.0048
2-NH$_2$-4,6-Me$_2$(**19**)	4.0658	3.9172	3.7749	4.0837	3.8372	3.8590	4.0020	3.9961	4.0014	4.0123	3.9454	3.9170
	π 1.0742	0.9422	0.8689	1.1075	0.9538	0.9876	1.0204	1.0036	1.0150	1.0054	1.0252	0.9788
N-Ph-*p*-QI(**20**)[a)]	3.9867	4.0408	3.7672	4.0442	4.0034	4.0174	3.9921	3.9975	3.9893	4.0138	3.8998	3.9024

a) *N*-Phenyl-*p*-benzoquinone monoimine numbered as for **1**.

orbital repulsion effects which contribute to ρ_I.[34)] In the case of the σ-inductive effect, the σ electron-deficient state of the carbon of interest induced by a σ-acceptor substituent decreases rapidly with an increasing number of intervening bonds between the substituent and the carbon.

The signs of the ρ_I values shown in Table 4 are consistent with those of the π-charge densities induced by the 2-substituents, except for the cases of C-6 and C-10a. Therefore, it is concluded that the main factors determining the ρ_I values, except for those of the carbon which is linked directly to the substituent, originate from π-inductive/field and orbital-repulsion effects rather than from a σ-inductive effect. A part of these polar effects spread along the π framework in the same manner as the resonance effect but with the different attenuation ratios; the observed negative or positive ρ_I values in Table 4 suggest that the polar effect of the 2-substituents such as NH_2 and OH groups cooperates with the corresponding resonance effect in upfield or downfield shifts of all the carbons other than C-4a, C-5a, and C-8, respectively. The absolute ρ_I values for the quinonoid carbons indicate the lowering of the polar effect on going from C-2 to C-4a in the clockwise direction as well as the anticlockwise one of C-1→C-4a.

The ρ_I value (−6.11) for C-2 of 3-substituted 2-cyclohexenones[32] is much less negative than that (−18.38) for C-1 of **1**. The π electron density of the substituted carbon of the former is decreased by the π acceptor carbonyl group. The lesser polar effect for the olefinic β carbon may be ascribed to the lesser orbital repulsion responsible for the more decreased π electron density of the substituted carbon.

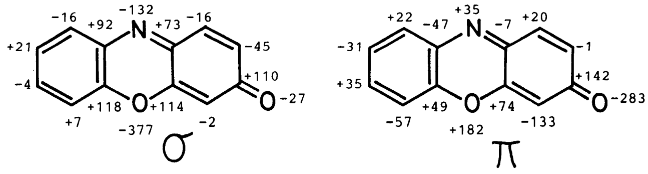
Judging from the SCS of 2-methyl, 4-methyl, and 2,4-dimethyl groups, the SCS values for all the carbons of 3*H*-phenoxazin-3-ones do not alter greatly in comparison with those of 3*H*-phenothiazin-3-ones. It is shown from the comparison between mono- and disubstituted analogues of methyl and ethyl groups on the 2- and 4-positions that an additivity relationship can be applied for 3*H*-phenoxazin-3-ones as well as for 3*H*-phenothiazin-3-ones.

*Electronic Structure of 3*H*-Phenoxazin-3-ones.* As Taft's DSP analysis for 3*H*-phenoxazin-3-ones shows, problems may arise during attempts to rationalize the ^{13}C chemical shifts on the basis of either π or the total electron densities alone. Table 5 lists the CNDO/2 π and total electron densities of 3*H*-phenoxazin-3-ones for the planar structure of their backbones. The ^{13}C chemical shifts gave a better correlation with the dual parameter system (r=0.940) composed of the π and σ electron densities than the π (r=0.908) or total electron density (r=0.919).

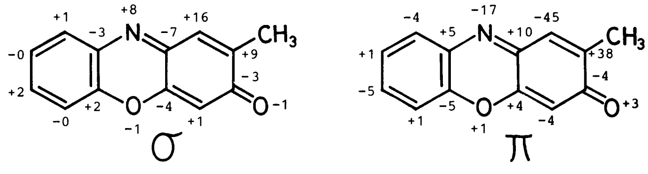
$$\delta = -100.29\sigma - 225.12\pi + 656.96 \qquad (r=0.940,\ n=180) \qquad (10)$$

Using INDO π and σ electron densities, the value of the correlation coefficient, r, for the chemical shifts of all the carbons of **1** is enhanced to be 0.955.[35] As Eq. 10 shows, the ^{13}C chemical shifts are much more sensitive to the π electron densities than the σ electron densities.

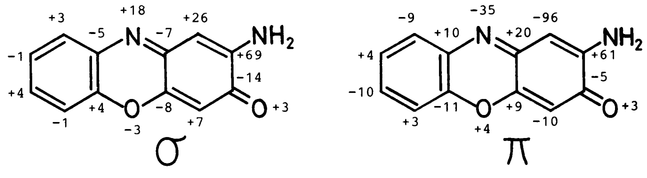
Figure 2 shows the CNDO/2 charge densities for **1** and the substituent-induced charge densities for **2**, **4**, and **11**. The π charge densities of all the carbons of **1** show alternative polarizations due to the presence of the electron-withdrawing carbonyl group and the π electron-donating ether oxygen. The CNDO/2 σ charge densities of their carbons of **1** indicate the partial positive charges on the carbons bonded to the heteroatoms and the lesser positive charges on C-6 and C-8. C-2 has the highest σ electron density among the twelve carbons of **1**.



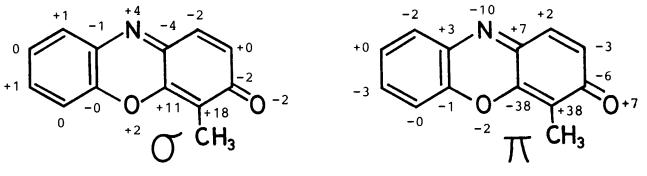
(a) Charge density of 1



(b) Substituent-induced charge density of 2



(c) Substituent-induced charge density of 4



(d) Substituent-induced charge density of 11

Fig. 2. CNDO/2 σ and π charge densities of **1** and substituent-induced σ and π charge densities. The values shown should be divided by 1000 to obtain electron charge units.

The delocalization of the lone-pair or pseudo-π electrons of the 2-substituent resulted in the increased π electron densities at C-1, C-3, C-5a, C-7, and C-9. The negative substituent-induced π charge density of C-4 suggests the polarization of the C-4–C-4a bond by the ether oxygen. The upfield shift of C-10a by the 2-substituent, contrary to the estimation from the CNDO/2 calculations, may be explained in terms of an enimine resonance between C-4 and C-10a.

From the correlation of the CNDO/2 π or σ charge density induced by the 2-substituents such as methyl, ethyl, amino, and hydroxyl groups with the parameters obtained by the principal factor method, Eq. 11 holds for all substituents with r=0.94—0.99;

$$10^4\Delta q_i = \mathrm{A}a_{i1}\sigma_i + \mathrm{B}a_{i4}\sigma_i + \mathrm{C} \qquad (11)$$

where Δq_i indicates the substituent-induced CNDO/2 π or σ charge density of the carbon i and A, B, and C are constants; a_{ij} and σ_i stand for the j th factor loading and the standard deviation of the chemical shifts for the carbon i shown in Table 3, respectively.

Table 6 lists the values of these constants for the 2-substituents. In the case of the π-electron system, A and

TABLE 6. THE CORRELATION OF THE SUBSTITUENT-INDUCED CNDO/2 π OR σ CHARGE DENSITIES OF 2-SUBSTITUTED 3H-PHENOXAZIN-3-ONES WITH THE FACTORS OBTAINED BY PRINCIPAL FACTOR METHOD[a)]

Substituent	π-Electron system				σ-Electron system			
	A	B	C	r	A	B	C	r
2-Me(**2**)	−39.36	65.30	28.19	0.973	11.35	64.83	−22.62	0.940
2-Et(**3**)	−47.54	75.01	33.96	0.973	15.34	45.89	−25.14	0.935
2-NH$_2$(**4**)	−80.92	68.92	60.90	0.973	10.40	307.61	−40.53	0.987
2-OH(**10**)	−91.85	51.78	66.87	0.978	2.59	527.20	−43.41	0.991

a) The constants of A, B, and C are equal to those in Eq. 11; r denotes correlation coefficient.

C become negatively and positively larger, respectively, with an increasing group-electronegativity of the 2-substituents. In the case of the σ-electron system, as σ_I of the 2-substituents increases, A decreases while B becomes larger; the more the group electronegativity of the 2-substituents increases, the more C increases negatively. The F_I—F_{IV} pair rather than the F_I—F_{II} or F_I—F_{III} pair gave a better correlation with the σ-electron densities as well as the π-electron densities. The $a_{ij}\sigma_i$ terms can be replaced by the transmission coefficients, obtained by a DSP treatment, with little change of r for the π-electron system but with a considerable lowering of r for σ-electron system.

In the case of **11**, the substituent-induced partial charges distribute in contrast with the polarization of **1** except for those of C-1 and C-4a for the σ system and those of C-1 and C-2 for the π system. The partial charges of C-4a is dispersed by the enone and the enimine resonances.

From a comparison of **2**, **11**, **16**, and the corresponding 3*H*-phenothiazin-3-ones, the significant difference for the relative abilities of the O and the S atoms to transmit the electronic effect of substituents was not observed because the π-electron transfer between the benzenoid and the quinonoid rings was carried out chiefly through the N atom.

The present work was supported by a Grant-in-Aid for Scientific Research No. 59550570 from the Ministry of Education, Science and Culture. Thanks are due to the Computer Center of the Institute for Molecular Science for its assistance in the CNDO/2 calculations.

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27) a) $F_{IV}=22.70\Delta\iota+1.13\sigma_R^+-3.72N-2.06$ ($r=0.949$, $n=7$); b) $F_{IV}=3.44\sigma_I+4.38\sigma_R^0+6.57B_1-8.59$ ($r=0.948$, $n=7$); c) $F_{IV}=14.16B_2-3.01B_2^2-0.80B_2^3-12.33$ ($r=0.942$, $n=8$).

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