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HAMMETT—TAFT CONSTANTS OF SUBSTITUTED 2- AND 4-QUINAZOLINYL GROUPS

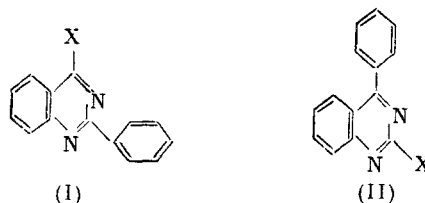S. G. Baram, O. P. Shkurko, and V. P. Mamaev*   UDC 543.422.25:451.67: 547.856.1

From the chemical shifts of the meta- and para-carbon atoms of the phenyl group in phenylquinazolines the σ_I and σ_R^0 constants of 2- and 4-quinazolinyl groups were determined. Correlation equations which enable us to calculate the σ constants of various substituted 2- and 4-quinazolinyl groups are proposed.

Until recently, data for the quantitative assessment of the electronic effects of quinazolinyl groups have been unknown. Our first publication contained preliminary, very general information on the Hammett—Taft constants of substituted 2- and 4-quinazolinyl groups, which was obtained by means of the ^{13}C NMR for the corresponding phenylquinazolines [1]. In the present work the determination of these constants was conducted with account taken of information that has appeared regarding the geometry of such a model structure.

For the calculation of σ_I and σ_R^0 constants of quinazolinyl groups we used the values of the chemical shifts of the m- and p-carbon atoms of the phenyl groups in the series of 4-substituted 2-phenylquinazolines (I) and 2-substituted 4-phenylquinazolines (II); here the substituted quinazolinyl group was regarded as a substituent in the benzene ring. The assignment of the signals in the ^{13}C NMR spectra of compounds (I) and (II) in acetone (Table 1) was conducted on the basis of published data for quinazoline [2, 3] and 4-phenylquinazoline [4].

(I)   (II)

X = H, Cl, OCH$_3$, N(CH$_3$)$_2$, CN.

In the calculation of σ constants of quinazolinyl groups we used the correlations found by us earlier [5] for monosubstituted benzenes, linking the values of σ_I and σ_R^0 constants of substituents with values of the relative chemical shifts of m- and p-carbon atoms of the benzene ring ($\Delta\delta C_m$ and $\Delta\delta C_p$):

$$\sigma_I = 0.034 + 0.315\Delta\delta C_m + 0.012\Delta\delta C_p,$$

$$\sigma_R^0 = 0.003 - 0.060\Delta\delta C_m + 0.045\Delta\delta C_p.$$

Here, in the values of $\Delta\delta C$ we introduced corrections of -0.23 ppm for C_m and -0.16 ppm for C_p in the case of the 2-phenylquinazolines (I) and -0.24 ppm for C_m and -0.22 ppm for C_p in the case of the 4-phenylquinazolines (II), which take account of the contribution of the diamagnetic anisotropy of the two rings of the quinazoline fragment in the magnetic shield-

*Deceased.

TABLE 1. ^{13}C Chemical Shifts of Substituted Phenylquinazolines in Acetone (δ, ppm)

Com-pound	Substi-tuent X	Quinazoline fragment								Phenyl ring				Other C atoms
		C^2	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	C_o	C_m	C_p	C_i	
(Ia)	H	161,33	161,64	128,31	128,36	135,17	129,14	151,42	124,66	129,24	129,33	131,42	138,98	
(Ib)	Cl	160,35	162,98	126,45	129,60	136,24	129,67	152,63	123,08	129,26	129,48	132,06	137,42	
(Ic)	OCH$_3$	160,22	167,74	124,04	127,42	134,47	128,65	152,54	115,83	129,09	129,09	131,29	138,86	54,50
(Id)	N(CH$_3$)$_2$	159,26	164,35	124,85	126,66	132,76	129,24	153,75	115,56	129,02	128,81	130,62	139,87	41,88
(Ie)	CN	161,25	144,52	125,81	130,06	137,16	130,83	152,48	122,90	129,28	129,67	132,34	137,34	115,28
(IIa)	H	156,11	169,43	128,39	129,44	135,25	130,34	152,70	124,39	131,57	130,01	131,43	138,87	
(IIb)	Cl	158,16	173,00	128,90	129,29	136,61	129,87	154,51	122,90	131,69	130,13	132,11	137,53	
(IIc)	OCH$_3$	164,00	173,16	126,45	128,59	135,59	128,76	154,57	121,30	131,40	129,97	131,54	138,62	55,62
(IId)	N(CH$_3$)$_2$	160,76	170,25	123,33	127,72	134,91	128,56	155,37	118,54	131,23	129,82	131,03	139,60	37,75
(IIe)	CN	141,92	171,41	129,02	130,50	137,07	132,37	152,48	124,82	131,83	130,30	132,47	137,34	118,21

TABLE 2. σ Constants of 4-Substituted 2-Quinazolinyl and 2-Pyrimidinyl Groups

Substituent X in quinazoline ring	$\Delta\delta C_m$	$\Delta\delta C_m^*$	$\Delta\delta C_p$	$\Delta\delta C_p^*$	σ_I	σ_R^0	Substituent X in pyrimidine ring	σ_I^{**}	σ_R^{0**}
H	0.25	0.02	2.34	2.18	0.07	0.10	H	0.05	0.10
Cl	0.40	0.17	2.98	2.82	0.12	0.12	Cl	0.11	0.13
OCH₃	0.01	−0.22	2.21	2.05	−0.01	0.11	OCH₃	0.00	0.11
N(CH₃)₂	−0.27	−0.50	1.54	1.38	−0.11	0.10	N(CH₃)₂	−0.10	0.10
CN	0.59	0.36	3.26	3.10	0.18	0.12	CN	0.18	0.14

*With correction for magnetic anisotropy.
**Data from [10].

TABLE 3. σ Constants of 2-Substituted 4-Quinazolinyl and 4-Pyrimidinyl Groups

Substituent X in quinazoline ring	$\Delta\delta C_m$	$\Delta\delta C_m^*$	$\Delta\delta C_p$	$\Delta\delta C_p^*$	σ_I	σ_R^0	Substituent X in pyrimidine ring	σ_I^{**}	σ_R^{0**}
H	0.93	0.69	2.35	2.13	0.28	0.06	H	0.21	0.09
Cl	1.05	0.81	3.03	2.81	0.32	0.08	Cl	0.25	0.12
OCH₃	0.89	0.65	2.46	2.24	0.27	0.06	OCH₃	0.19	0.10
N(CH₃)₂	0.74	0.50	1.95	1.73	0.21	0.05	N(CH₃)₂	0.08	0.08
CN	1.22	0.98	3.39	3.17	0.38	0.09	CN	0.34	0.12

*With correction for magnetic anisotropy.
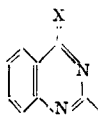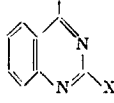**Data from [10].

ing of the carbon atoms of the benzene ring. The additive assessment of the influence of the two rings in the quinazoline is based on calculated data on magnetic anisotropy for such condensed aromatic and heteroaromatic systems [6]. An approximate assessment of these anisotropy corrections was made by the method of Johnson and Bovey [7] with the use of the geometric parameters established for 6-isopropyl-2,4-diphenylquinazoline [8]. Apart from this, in the assessment of all the corrections indicated above we took account of the coefficient 0.78 recommended for use in ^{13}C NMR spectroscopy [9]. An important feature of the structures under examination consists in the different angles of rotation of the benzene rings relative to the plane of the quinazoline nucleus. Whereas the 2-phenyl group and the quinazoline nucleus are practically coplanar (the angle of rotation does not exceed 4°), the torsion angle for the 4-phenyl group attains ~64°. Hence, the anisotropy correction for the C_m atoms of the benzene ring in 4-phenylquinazolines differs little from the analogous correction in the case of 2-phenylquinazolines despite the greater closeness of the 4-phenyl group to the annelated benzene ring in quinazoline. The chemical shifts $\Delta\delta C_m$ and $\Delta\delta C_p$ for compounds (I) and (II), recalculated relative to the signal of benzene in acetone (129.08 ppm) and corrected to take account of anisotropy corrections, are given in Tables 2 and 3. On the basis of these chemical shifts we calculated the σ constants of unsubstituted (Quiz) and substituted (QuizX) quinazolinyl groups, comparable in magnitude with the constants of the corresponding 2- and 4-pyrimidinyl groups (Tables 2 and 3).

Comparing in pairs the values of σ_R^0 for 2- and 4-quinazolinyl groups of the same type, we can observe a tendency for some lowering of the −M effects of the latter, which probably arises from the rotation of the 4-phenyl group because of steric hindrance and of decrease in the overlap of the π-orbitals of the benzene and quinazoline rings. The difference in induction constants for 2- and 4-quinazolinyl groups is more substantial. Whereas 4-substituted 2-quinazolinyl groups change from weakly donating to weakly accepting, depending on the substituents with a scatter of 0.39 units on the σ_I scale, 2-substituted 4-quinazolinyl groups have stronger electron-acceptor properties, but the scatter of values of σ_I is less (0.17). An analogous situation is found when we compare constants for 2- and 4-pyrimidinyl groups. It is probable that the cause of the stronger induction effect of 4-quinazolinyl

TABLE 4. Parameters of Correlation Equations

$$\sigma_I \text{ (Quiz X)} = \sigma_I \text{ (Quiz)} + a\sigma_I (X) + b\sigma_R^0 (X) \qquad \text{(I)}$$

$$\sigma_R^0 \text{ (Quiz X)} = \sigma_R^0 \text{ (Quiz)} + a\sigma_I (X) + b\sigma_R^0 (X) \qquad \text{(II)}$$

Equation	Group	a	b	r	s
(I) (II)	(quinazoline 4-X structure)	0.17 0.05	0.30 0.03	0.979 0.977	0.031 0.003
(I) (II)	(quinazoline 2-X structure)	0.16 0.06	0.14 0.03	0.992 0.992	0.011 0.003

groups than of 2-quinazolinyl groups lies in the different directions of the dipole moment of the quinazoline fragment relative to the phenyl groups and therefore in the different contributions of the electrostatic component in the overall induction effect for these groups [11].

It was shown earlier [12] that the electronic effects of complex substituents can be explained in terms of the effects of the separate structural fragments by means of simple correlation equations. This approach was extended to substituted 2- and 4-quinazolinyl groups. The parameters found for Eqs. (I) and (II) (Table 4) enable us to calculate values of σ constants for various 2- and 4-quinazolinyl groups.

A general consideration of the electronic effects of substituted 2- and 4-quinazolinyl groups leads to the conclusion that there is no appreciable influence of the annelated benzene ring on the Hammett–Taft constants of 2-pyrimidinyl groups, but there is a small strengthening of the induction effect in the case of 4-pyrimidinyl groups (see Tables 2 and 3).

EXPERIMENTAL

The ^{13}C NMR spectra were recorded at ~25°C on a Bruker AC-200 spectrometer (50.32 MHz). For the determination of ^{13}C NMR spectra we used solutions of the substances in acetone, concentration 0.2 M; internal standard TMS. For the stabilization of the resonance conditions we added $(CD_3)_2CO$ (~5%).

4-Methoxy-2-phenylquinazoline (Ic). To a solution of 4.81 g (20 mmoles) of 4-chloro-2-phenylquinazoline (Ib) in 40 ml of abs. CH_3OH a solution of CH_3ONa in CH_3OH [prepared from 0.46 g (0.02 g-atom) of Na in 5 ml of absolute CH_3OH] was added. The reaction mixture was boiled for ~1 h. The progress of reaction was followed by means of chromatography on Silufol (benzene:CCl_4 2:1). The mixture was evaporated to dryness, the residue was treated with 20 ml of H_2O and extracted with ether, and the extract was dried over anhydrous $MgSO_4$. Ether was evaporated, and the residue was vacuum-sublimed. Yield 4.51 g (95%), mp 66-67°. Found, %: C 76.3, H 5.20, N 11.8. $C_{15}H_{12}N_2O$. Calculated, %: C 76.3, H 5.21, N 11.9.

2-Methoxy-4-phenylquinazoline (IIc) was prepared from 2-chloro-4-phenylquinazoline (IIb) by a procedure analogous to that for (Ic). Yield 90%, mp 86-87°. Found, %: C 76.2, H 5.05, N 11.8. $C_{15}H_{12}N_2O$. Calculated, %: C 76.3, H 5.12, N 11.9.

4-(Dimethylamino)-2-phenylquinazoline (Id). To a solution of 2.41 g (10 mmoles) of (Ib) in 50 ml of dry acetone 20 ml of dry acetone containing 0.9 g (20 mmoles) of $NH(CH_3)_2$ was added. The progress of reaction was followed chromatographically on Silufol ($CHCl_3$). The reaction mixture was evaporated to dryness, the residue was dissolved in benzene, and the solution was passed through a column of Al_2O_3 with a Brockmann activity of II; eluent benzene. The solution was evaporated, and the residue was vacuum-sublimed. Yield 2.42 g (97%); mp 66-68°C. Found, %: C 77.1, H 6.04, N 16.7. $C_{16}H_{15}N_3$. Calculated, %: C 77.1, H 6.06, N 16.9.

2-(Dimethylamino)-4-phenylquinazoline (IId) was prepared from (IIb) by a procedure analogous to that for (Id). After the evaporation of the reaction mixture, the residue was crystallized from petroleum ether (bp 70-100°C) and vacuum-sublimed. Yield 95%, mp 125-126°C. Found, %: C 77.1, H 6.08, N 16.7. $C_{16}H_{15}N_3$. Calculated, %: C 77.1, H 6.06, N 16.9.

Trimethyl(2-phenyl-4-quinazolinyl)ammonium Chloride (III). To a solution of 2.41 g (10 mmoles) of (Ib) in 70 ml of dry acetone, 20 ml of dry acetone containing 1.77 g (30 mmoles) of $N(CH_3)_3$ was added. The mixture was left overnight. The precipitate formed was filtered off, washed with acetone, and dried. Yield 2.74 g (91%). Found, %: C 68.0, H 6.15, Cl 11.9, N 13.9. $C_{17}H_{18}ClN_3$. Calculated, %: C 68.1, H 6.05, Cl 11.8, N 14.0.

Trimethyl(4-phenyl-2-quinazolinyl)ammonium chloride (IV) was prepared from (IIb) by a procedure analogous to that for (III). Yield 90%. Found, %: C 68.2, H 5.98, Cl 11.9, N 14.1. $C_{17}H_{18}ClN_3$. Calculated, %: C 68.1, H 6.05, Cl 11.8, N 14.0.

4-Cyano-2-phenylquinazoline (Ie). A mixture of 1.5 g (5 mmoles) of (III), 0.65 g (10 mmoles) of KCN, and 10 ml of H_2O was stirred for 1 h at 70°C and then cooled to 20°C. The precipitate was filtered off, washed with H_2O, vacuum-dried, and recrystallized from acetone. Yield 0.83 g (71%); mp 166-168°C. Found, %: C 78.1, H 3.83, N 18.2. $C_{15}H_9N_3$. Calculated, %: C 77.9, H 3.92, N 18.2.

2-Cyano-4-phenylquinazoline (IIe) was prepared from (IV) by a procedure analogous to that for (Ie). Yield 72%, mp 120-121°C. Found, %: C 77.7, H 3.81, N 18.0. $C_{15}H_9N_3$. Calculated, %: C 77.9, H 3.92, N 18.2.

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