EFFECT OF FLUORINE-SUBSTITUTION ON BASICITY OF BENZO[*h*]QUINOLINE, BENZO[*f*]QUINOLINE AND QUINOLINE

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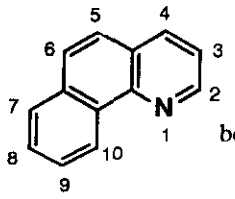
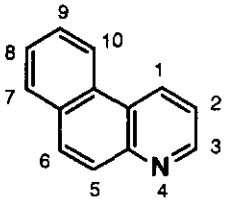
Abstract -The effect of fluorine-substitution on the acid-dissociation constant was examined using 19 types of mono- and difluorinated derivatives of benzo[*h*]quinoline, benzo[*f*]quinoline and quinoline. Decreases in pKa were induced by fluorine substitution and were dependent on the number of bonds between the substituent F atom and the basic N atom, whereas pKa-increases were induced by a substituent F atom spatially interacting with the basic N atom. The spatial interaction between F and N was analyzed by means of a semiempirical molecular orbital method MOPAC PM3 .

We investigated fluorine-substituted heteroaromatic compounds with special attention to their biological behavior. The covalent and van der Waals radii of the fluorine atom are not much larger than those of the hydrogen atom, so that they often exert so-called mimic effects on interactions with biological molecules. However, replacement of hydrogen with fluorine results in not only changes in electron-density distribution within the molecule but also in electric repulsive/attractive interactions with intra/intermolecular environments. These changes may significantly affect such interactions as those between an enzyme and its substrate or a receptor and its ligand. In addition, metabolism of xenobiotics, including drugs, food-additives, and other environmental chemicals, are sometimes crucially altered by fluorine-substitution, rendering these substances generally resistant to enzymic oxidations at the site of substitution. This may produce either desirable or undesirable modifications of the biological activity. As we previously reported,[1] one example of this is the abolishment of genotoxicity from carcinogenic and mutagenic quinoline by fluorine-substitution at position-3. In a serial study along this line, we synthesized fluorinated derivatives of benzo[*h*]quinoline (B[*h*]Q), benzo[*f*]quinoline (B[*f*]Q), and quinoline. This paper provides a collective data of the acid-dissociation constants of the fluorinated derivatives so far synthesized. Note that the acid-dissociation constant is for the "protonated" bases although the term "protonated" is omitted in this text. A discussion is made on the spatial effect of a fluorine substituent on its neighboring basic nitrogen, taking into consideration the total electronic energy calculated using a semiempirical molecular orbital MOPAC PM3 method. Data are included in Figure 1.

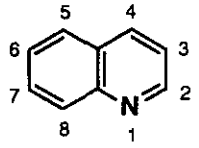
B[*h*]Q and B[*f*]Q have pKa's of 4.3 and 4.7, respectively. The 0.4 units difference between these two values may be mainly due to destabilization of the protonated benzo[*h*]quinoline in which the two hydrogens of C^{10}-H and N^{+}-H come into proximity in a bay-like region resulting in a severe steric hindrance. The pKa of quinoline without such a steric hindrance is 4.8 similar to that of B[*f*]Q.



benzo[*h*]quinoline (B[*h*]Q)



benzo[*f*]quinoline (B[*f*]Q)



quinoline

Derivatives	pKa (± SD)	ΔpKa*	No. of bonds between N and F
B[*h*]Q	4.34 ±0.10	±0.0	
3-F-	1.96 ±0.01	−2.4	*3 bonds*
5-F-	3.21 ±0.08	−1.1	*4 bonds*
6-F-	3.58 ±0.05	−0.8	*5 bonds*
7-F-	3.53 ±0.10	−0.8	*5 bonds*
9-F-	3.67 ±0.16	−0.7	*5 bonds*
3,6-diF-	1.51 ±0.08	−2.8	
5,6-diF-	2.34 ±0.06	−2.0	
7,10-diF-	4.16 ±0.09	−0.2	
B[*f*]Q	4.72 ±0.15	±0.0	
2-F-	2.49 ±0.10	−2.2	*3 bonds*
7-F-	4.53 ±0.13	−0.2	*6 bonds*
10-F-	4.34 ±0.19	−0.4	*5 bonds*
7,10-diF-	4.27 ±0.11	−0.5	
Quinoline	4.93 ±0.35	±0.0	
3-F-	2.51 ±0.14	−2.4	*3 bonds*
5-F-	3.69 ±0.16	−1.2	*4 bonds*
6-F-	4.03 ±0.13	−0.9	*5 bonds*
8-F-	3.36 ±0.12	−1.5	*3 bonds*
5,8-diF-	2.16 ±0.19	−2.7	
6,7-diF-	3.84 ±0.06	−1.1	
6,8-diF-	2.54 ±0.19	−2.4	

Figure 1 Fluorinated Derivatives of Benzo[*h*]quinoline, Benzo[*f*]quinoline, and Quinoline and Their pKa Values Measured at Room Temperature (* Deviations from the respective parent base)

Dependence of pKa on the number of bonds between the basic N atom and the substituent F atom

The pKa value is primarily determined by the difference in thermodynamic stability between the protonated and non-protonated structures of a base. With respect to a series of structurally related compounds, the stability (i.e., free energy) difference may be based mainly on the enthalpy change for the structures involved, because changes in the solvation and entropy are common in their acid dissociation equilibria.[2] Since activated structures are not substantially involved in establishing the equilibria, the electronic effect of a substituent may be mainly due to σ-bonding electrons (i.e., inductive effect) and secondarily to π-bonding electrons (i.e.,

resonance effect), as well as a result of H-bonding and/or electrostatic field interaction in favorable/unfavorable steric environments. With these considerations in mind, the dependence of pKa on the number of bonds between the basic N and substituent F atoms was examined. An averaged deviation of pKa of a mono-fluorinated derivative from that of its respective parent base was defined as the substituent effect, reflecting the number of bonds involved between the F and N atoms, for example, the "*3-bond* effect". Several examples are given for the "*5-bond* effect" of a substituent fluorine as seen in Figure 1. Most of these range from −0.9 to −0.7. A smaller value of −0.4 is seen with 10-F-B[*f*]Q in which the F-substituent is sterically hindered by a hydrogen at position-1, (*in a bay-region*). With regard to the "*4-bond* effect", −1.1 and −1.2 are obtained from 5F-B[*h*]Q and 5-F-Q, respectively. Three values of the "*3-bond* effect" are presented, all of which fall into a range of −2.4 to −2.2. A fairly deviated value of −1.5 is seen with 8-F-Q in which F is at a *peri*-position to N−H in the protonated form and to a lone-pair of electrons in the non-protonated form, which likely results in stabilization by means of H-bonding/electrostatic field interaction and electrostatic repulsion, respectively. The only one value available for the "*6-bond* effect" was −0.2.

Additivity of the fluorine-substitution effect on pKa in the difluorinated derivatives

It is tentatively assumed that the effect of fluorine-substitution is simply cumulative in difluorinated derivatives unless an electronic disturbance should arise from steric interaction by the substitution. As shown in Table I, fairly substantial additivity is achieved when the following magnitudes of substitution effects are assumed for the calculation of additive values:

"*3-bond* effect" = −2.3; "*4-bond* effect" = −1.2; "*5-bond* effect" = −0.8; "*6-bond* effect" = −0.2;
"*bay-region* effect" = +0.7 ["*4-bond* effect" −1.2 + "*bay*-spatial effect" +1.9];
"*peri* effect" = −1.5 ["*3-bond* effect" -2.3 + "*peri*-spatial effect" +0.8];
"5-bond* effect" for 10-F and 1-H of B[*f*]Q = −0.4.

Assuming that pKa of 7,10-diF-B[*h*]Q (4.2) may be additively calculated with a *5-bond* effect (−0.8) due to 7-F atom and a "*bay-region effect*" which consists additively of a "*4*-bond effect" (−1.2) and a certain spatial effect, the "*bay*-spatial effect" may be calculated as [4.2 = 4.3 + (−0.8) + (−1.2) + (*bay*-spatial effect)], hence it may be estimated to be +1.9. In other words, the "*bay-region* effect" includes both a pKa-decreasing "*4-bond* effect" and a pKa-increasing spatial effect. As a whole, the "*bay-region* effect" becomes 0.7. With regard to the "*peri* effect", pKa of 8-F-quinoline (3.4) may be presented by [4.9 + (−2.3 for "*3-bond* effect") + (*peri*-spatial effect)], hence "*peri-spatial* effect" may become +0.8. That is, the "*peri-* effect" (−1.5) also consists of both a pKa-decreasing "*3-bond* effect" and a pKa-increasing spatial effect. Fluorine atom at position-10 and H at position-1 in 10-F-B[*f*]Q are in a spatial proximity, so that a certain spatial interaction term might be included. Therefore, a different value, −0.4, should be given to the "5-bond* effect" in such a situation as in 10-F-B[*f*]Q.

Table I shows the pKa values calculated using the F-substitution effects estimated above. Fairly good agreements were found between the found and the observed values. Among them, an appreciable deviation was found for 6,7-diF-quinoline, in which one fluorine atom is located in *ortho*-position of the other fluorine, possibly producing an electronic distortion. In general, it is probable that each of fluorine-substitutions may affect the basicity of heteroaromatics in an additive manner, unless steric hindrance between the aromatic hydrogens and/or other substituents is introduced by fluorine-substitution.

Table I Effect of Fluorine-Substitution on pKa of B[*h*]Q's, B[*f*]Q's, and Quinolines Provided that pKa Primarily Depends on the Number of Bonds between the basic N atom and the F atom

Compound	pKa observed	pKa calculated	ΔpKa	F-Effects used for calculation# (sum of the effects)
B[*h*]Q	4.3	(4.3)	—	
3-F-	2.0	2.0	±0.0	*3-bond* effects (−2.3)
5-F-	3.2	3.1	+0.1	*4-bond* effects (−1.2)
6-F-	3.6	3.5	+0.1	*5-bond* effect (−0.8)
7-F-	3.5	3.5	±0.0	*5-bond* effect (−0.8)
9-F-	3.7	3.5	+0.2	*5-bond* effect (−0.8)
3,6-diF-	1.5	1.2	+0.3	*3&5-bond* effects (−3.1)
5,6-diF-	2.3	2.3	±0.0	*4&5-bond* effects (−2.0)
7,10-diF-	4.2	4.2	±0.0	*5-bond* effect, *bay*-effect (−0.1)
B[*f*]Q	4.7	(4.7)	—	
2-F-	2.5	2.4	+0.1	*3-bond* effects (−2.3)
7-F-	4.5	4.5	±0.0	*6-bond* effects (−0.2)
10-F-	4.3	4.3	±0.0	*5-bond** effects (−0.4)
7,10-diF-	4.3	4.1	+0.2	*6-bond* effect, *5-bond** effect (−0.6)
Quinoline	4.9	(4.9)	—	
3-F-	2.5	2.6	−0.1	*3-bond* effects (−2.3)
5-F-	3.7	3.7	±0.0	*4-bond* effects (−1.2)
6-F-	4.0	4.1	−0.1	*5-bond* effect (−0.8)
8-F-	3.4	3.4	±0.0	*peri*-effect (−1.5)
5,8-diF-	2.2	2.2	±0.0	*4-bond* effect, *peri*-effect (−2.7)
6,7-diF-	3.8	2.9	+0.9*	*5&4-bond* effect* (−2.0)
6,8-diF-	2.5	2.6	−0.1	*5-bond* effect, *peri*-effect (−2.3)

Calculated pKa's are derived by adding the sum of the following substituent effects to pKa values of the respective parent bases: 4.3, 4.7, and 4.9 for B[*h*]Q, B[*f*]Q, and quinoline, respectively. Substituent effects used for calculation are listed in the text.

* Two F atoms at the *ortho* position may mutually interact, resulting probably in a distortion from the additivity.

Evaluation of the "*bay-region* effect" by means of a semiempirical molecular orbital MOPAC *PM3 method*

Total energy (sum of electronic energy and core-core repulsion) was calculated for the protonated and non-protonated structures of fluorinated benzo[*h*]quinolines, some of which were not yet available for the present study. Table II shows the calculated total energies of fluorinated B[*h*]Q's as well as the energy gained by protonation of each derivative. It may be worth noting that the protonated structure includes one more hydrogen in the molecule than does the non-protonated structure, hence the total energies of the former have larger negative values, although the cationic structure is much more unstable than the neutral form of the non-protonated structure. In order to compare stabilities of the protonated *versus* non-protonated structures among fluorinated B[*h*]Q's, the energy gains obtained by protonation of the derivatives are referred to that of the parent hydrocarbon B[*h*]Q, as listed in Table II where it is termed "relative energy gain referred to B[*h*]Q". In Figure 2, the observed pKa values are plotted *versus* the relative energy gain, and a fairly good linearity is evident.

$$pKa = 4.48 - 8.30 \times [\text{relative energy gain}], \quad \text{where } r^2 = 0.932.$$

The other two series of heteroaromatics, B[*f*]Q's and quinolines, gave poorer linearities, possibly because of the smaller number of samples available. In principle, strict linearity could not be met in this manner because of complete neglect of the entropy term, which would have reflected stabilization of the cation by solvation and destabilization of the cluster structure of water by dissolution of the substrate.[2] These entropy terms may depend on the position of the fluorine atom substituted.

Since a fairly good correlation has been obtained for a series of B[*h*]Q derivatives, the "*bay-region* effect" was tentatively correlated with certain electronic features suggested from molecular orbital calculations. Changes in total energy induced by fluorine-substitution were compared among the protonated and non-protonated structures, respectively, of fluorinated B[*h*]Q's, as shown in Figure 3. Among the non-protonated derivatives, the 10-F derivative is the most unstable, probably because of an electrostatic repulsion between an electronegative fluorine and the lone-paired electrons of the nitrogen, both of which are located in a bay region. On the other hand, this positional isomer is the most stabilized of the protonated structures, probably as a result of H-bonding or electrostatic field interaction between the F atom at position-10 and the cationic N-H hydrogen, both of which are placed within a van der Waals radius, leading to stabilization of the protonated structure. As a result, the energy difference between the protonated and non-protonated forms of the 10-F isomer is the smallest among those of all other positional isomers, even smaller than the parent B[*h*]Q itself, in spite of the presence of an electronegative F at a "*4-bond*" distance from the N atom, as shown in Figure 4. Other information from the molecular orbital calculation supports the above. The electron density on the fluorine atom of the 10-F isomer is the largest of those of all other isomers in the protonated form, whereas it is the smallest of those with the non-protonated form, as shown in Figure 5. Thus, the lone-paired electrons on the nitrogen restrained electron-flow from the π-orbital to the fluorine atom in the non-protonated structure,

whereas H-bonding or electrostatic interaction with the cationic N-H group promoted an electron-flow from the π orbital to the fluorine atom. These results suggest that the MOPAC PM3 program for a semiempirical molecular orbital calculation may be applied to a semiquantitative assessment of the acid dissociation equilibria to the extent that is described here.

Table II Relative Energy Gain by Protonation of Fluorinated B[*h*]Q's Referred to the Parent Hydrocarbon Calculated Using a Semiempirical Molecular Orbital Method MOPAC PM3

Compound	Total energy* Protonated base	Total energy* Free base	Energy gain by protonation	Relative energy gain referred to B[h]Q	pKa observed	(pKa calcd)#
B[*h*]Q	-1849.0079	-1840.1183	-8.8900	±0.000	4.3	(4.5)
2-F-	-2273.6927	-2265.0768	-8.6159	+0.274		(2.2)
3-F-	-2273.6239	-2264.9645	-8.6594	+0.231	2.0	(2.6)
4-F-	-2273.6834	-2264.9542	-8.7292	+0.161		(3.1)
5-F-	-2273.6813	-2264.9625	-8.7188	+0.171	3.2	(3.1)
6-F-	-2273.7223	-2264.9590	-8.7633	+0.127	3.6	(3.4)
7-F-	-2273.7270	-2264.9613	-8.7657	+0.125	3.5	(3.4)
8-F-	-2273.7636	-2265.0102	-8.7534	+0.137		(3.3)
9-F-	-2273.7712	-2265.0031	-8.7681	+0.122	3.7	(3.5)
10-F-	-2273.8448	-2264.8673	-8.9775	-0.088		(5.2)
3,6-diF-	-2698.3337	-2689.7982	-8.5355	+0.355	1.5	(1.5)
5,6-diF-	-2698.3780	-2689.7829	-8.5951	+0.295	2.3	(2.0)
7,10-diF-	-2698.5425	-2689.6902	-8.8523	+0.038	4.2	(4.2)

* Total energy (sum of electronic energy and core-core repulsion) in an eV unit.
# (pKa calcd) were calculated by the correlation equation (Figure 2).

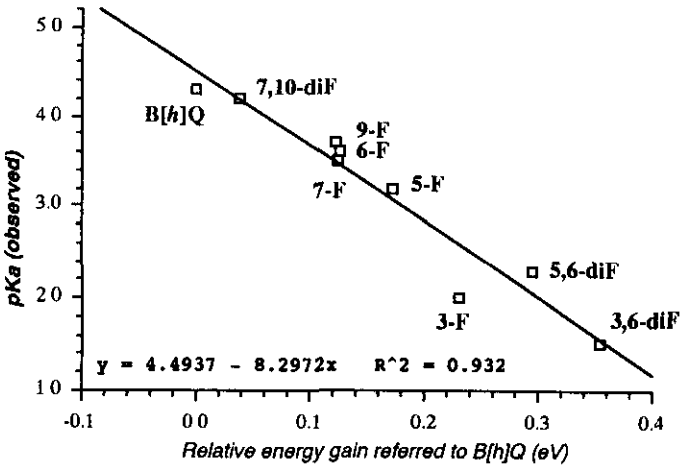


Figure 2 Correlation of Relative Energy Gain by Protonation with Observed pKa

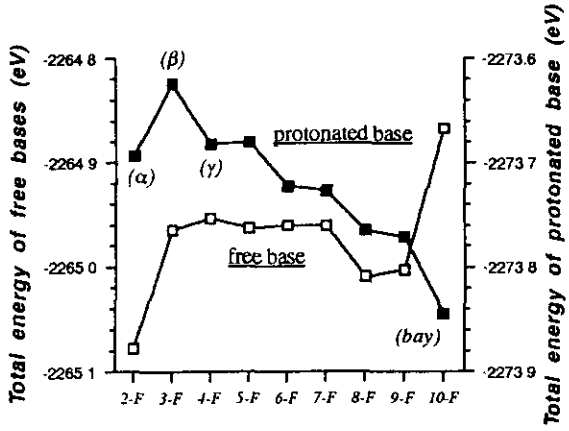


Figure 3 Total Energy of Protonated and Free Forms of Mono-Fluorinated B[*h*]Q's

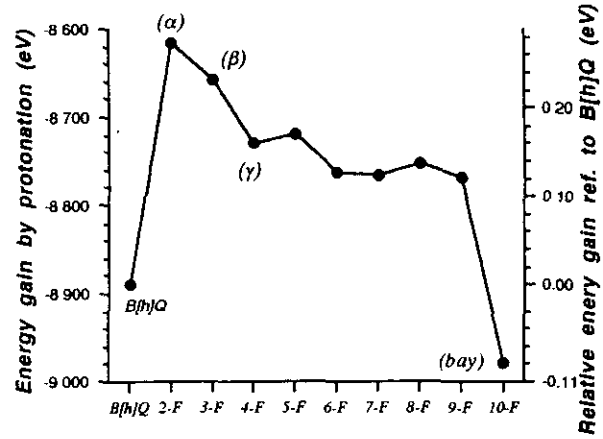


Figure 4 Relative Energy Gain of B[*h*]Q's

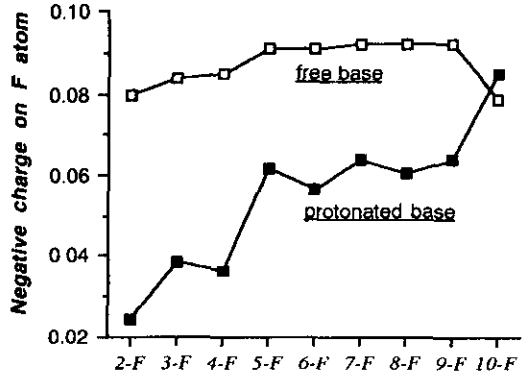


Figure 5 Negative Charge on F of Protonated and Free Base of Mono-Fluorinated B[*h*]Q's

EXPERIMENTALS

All fluorinated derivatives examined were synthesized in our laboratory. Methods of syntheses and structural identification are to be published elsewhere.[3] The starting materials, B[*h*]Q, B[*f*]Q and quinoline, were purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo). Molecular orbital calculation was carried out using MOPAC Ver. 6.01 (Version 6: Stewart, J. J. P. QCPE Bull. 1989, 9, 10; revised as Version 6.01 by Hirano, T. JCPE Newsletter, 1991, 2, 26), in which calculation method was PM3.

For pKa measurement, the sample to be examined was dissolved in 1 N HCl at a concentration range of 1-4 $\mu g/ml$. The pH of the solution was adjusted by addition of aqueous NaOH. UV absorbance was measured at 4 wave lengths (2 λ_{max}'s and 2 λ_{min}'s for each sample). The pKa value was calculated as follows.

$$pKa = pH - \log\{(Ap - A)/(A - Af)\}$$

where Ap is the absorbance at pH 0.0 (for the protonated form), Af is the one at pH 10.0 (for the non-protonated from), and A is the observed absorbance at each pH value of the solution examined.

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