SUBSTITUENT EFFECT OF THE FLUORINE ATOM ON ELECTROPHILIC DEUTERATION OF BENZO[*h*]QUINOLINE

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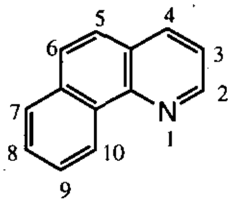
Abstract — Substituent effect of the fluorine atom on electrophilic substitution using the deuterium cation was examined by treating monofluorinated derivatives of benzo[*h*]quinoline with 96% D_2SO_4 at 80°C. The effect of the fluorine atom could not simply be explained by potent electron-withdrawing I-effect and electron-donating R-effect. The observed reaction rates were not simply correlated either with the stability of the σ–complexes estimated by a semiempirical molecular orbital MOPAC PM3 method. A fair correlation was found but not sufficiently for quantitative prediction of the rate.

Our recent attention has focused on the role of the fluorine atom in the chemical, physico-chemical, and biological behavior of the biologically active hetero-aromatics.[1-3] The covalent and van der Waals radii of fluorine atom are not much greater than those of hydrogen atom, so that they often exert a so-called mimic effect in interactions with biological molecules. However, replacement of hydrogen with fluorine creates changes not only in the electron distribution within the molecule but also affects electric repulsive/attractive interactions within intra/intermolecular environment, which may significantly affect enzyme-substrate interactions, receptor-substrate interactions, and other systems. For example, metabolism of aromatic xenobiotics may be critically affected by fluorine-substitution, such that the substitution site becomes generally resistant to enzymatic oxidation leading to either desirable or undesirable modification in biological activity.[4] As we previously reported,[1] the genotoxicity of carcinogenic and mutagenic quinoline derivatives was abolished by fluorine-substitution at position-3 of the quinoline nucleus. The aim of this study was to obtain a basic knowledge of how a substituent fluorine atom influences the electrophilic reactivity of the aromatic ring, especially at distant locations, and how reliable recent molecular orbital methods may be for estimating the reaction rate, i.e., the stability of the rate-determining activated structures. It is well known that electrophilic substitution reactions of aromatic compounds proceed *via* the σ–complex with an attacking electrophile and that the stability of the complex is the major rate-determinant. With recent progress in computational methods, estimation of the stability of activated structures such as σ–complexes has become more and more reliable, even for those including heteroatoms in the molecule. In order to evaluate the substitution effect of fluorine in electrophilic aromatic substitutions, fluorinated benzo[*h*]quinolines (B[*h*]Q's) recently synthesized in our laboratory[5] were subjected to deuteration in 96% D_2SO_4 at 80°C. The results were discussed in connection with the stability estimated from the energy gain by σ–complex formation with the aid of a semiempirical molecular orbital MOPAC 93 PM3 program.



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

RESULTS

Pseudo-first order rate constants (min^{-1}) were calculated using nmr spectra from a time-course study of changes in the areal intensity of each proton in question. Deuteration of hydrogens noted at positions–5, -6, -7, and -10, but not at positions–2, -3, and -4 under the reaction conditions employed. The hydrogens at positions–8 and -9 underwent deuteration in B[*h*]Q and its 3-F and 5-F derivatives, but the nmr signals of these protons unfortunately overlapped. Therefore, quantitative comparisons of deuteration rates were made only among hydrogens at positions–5, -6, -7, and -10 in B[*h*]Q and their fluorinated derivatives. The results are summarized in Table I. B[*h*]Q itself underwent deuteration at the rates in decreasing order as follows: 7-H > 5-H ≈ 10-H > 6-H.

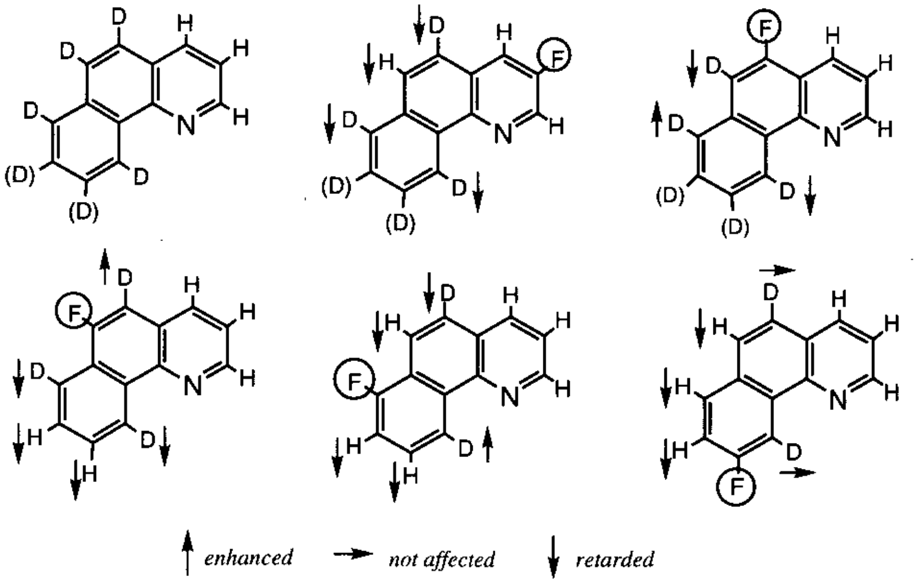
Substituent Effect of the Fluorine Atom on Electrophilic Deuteration of B[*h*]Q

Enhancement and retardation of deuteration by F atom substitution are qualitatively illustrated in Scheme 1. **3-F-B[*h*]Q**: The 3-F atom appreciably retarded the exchange of all the ring hydrogens observed. **5-F-B[*h*]Q**: The 5-F atom retarded the exchange of 6-H and 10-H, whereas it enhanced that of 7-H. **6-F-B[*h*]Q**: The 6-F atom considerably retarded the exchange of 7-H and 10-H, whereas it appreciably enhanced that of 5-H. **7-F-B[*h*]Q**: The 7-F

Table I *Pseudo-first order rate constants at 80°C for H-D exchanges of ring hydrogens at positions–5, -6, -7, and -10 of B[h]Q bearing a F atom at positions–3, -5, -6, -7, or -9 in sulfuric acid-d_2*

	H-5		*H-6*		*H-7*		*H-10*	
Substi-tuent	kobs(10^{-3}/min) (rel.kobs)[a]	half life $T_{1/2}$ (min)	kobs(10^{-3}/min) (rel.kobs)[a]	half life $T_{1/2}$ (min)	kobs(10^{-3}/min) (rel.kobs)[a]	half life $T_{1/2}$ (min)	kobs(10^{-3}/min) (rel.kobs)[a]	half life $T_{1/2}$ (min)
none	17.16 (1.00)	40.4	2.16 (1.00)	321.2	55.45 (1.00)	12.5	16.82 (1.00)	41.2
3-F	5.42 (0.32)	128.2	0.00 (0.00)	∞	24.58 (0.44)	28.2	6.14 (0.37)	112.8
5-F			0.95 (0.44)	729.3	80.60 (1.45)	8.6	4.63 (0.28)	149.8
6-F	45.90 (2.68)	15.1			2.37 (0.04)	292.9	4.88 (0.29)	141.9
7-F	1.08 (0.06)	641.4	0.00 (0.00)	∞			52.51 (3.12)	13.2
9-F	14.23 (0.83)	48.7	0.00 (0.00)	∞	0.00 (0.00)	∞	17.77 (1.06)	39.0

a) Rate constants relative to the rate of the hydrogen at the corresponding position of non-substituted B[*h*]Q.

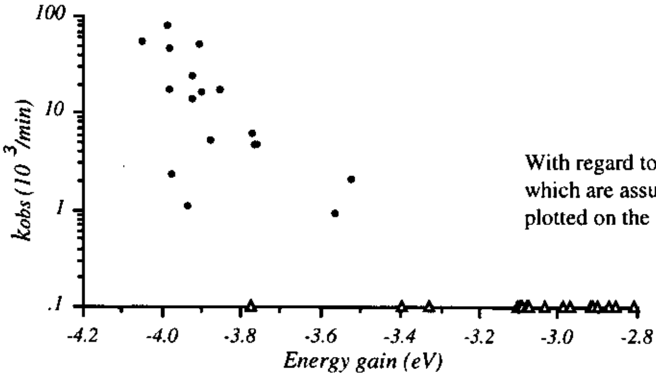


Scheme 1 *Effects of Fluorine Substitution on Electrophilic Deuterations of B[h]Q's*

atom remarkably retarded the exchange of 5-H and 6-H, whereas it enhanced the exchange of 10-H. **9-F-B[*h*]Q**: The 9-F atom retarded exchanges of all hydrogens except for 10-H. As seen in Table I, fluorine substitution brought about, in general, an appreciable retardation of deuterium substitutions to a more or less extent. Exceptions were found in the exchange of 7-H, 5-H, and 10-H which were moderately enhanced by fluorine substitution at positions-5, 6-, and 7, respectively. It does not appear that the substituent effect of the F atom could be simply explained by its potent electron-withdrawing I-effect and an electron-donating R-effect.

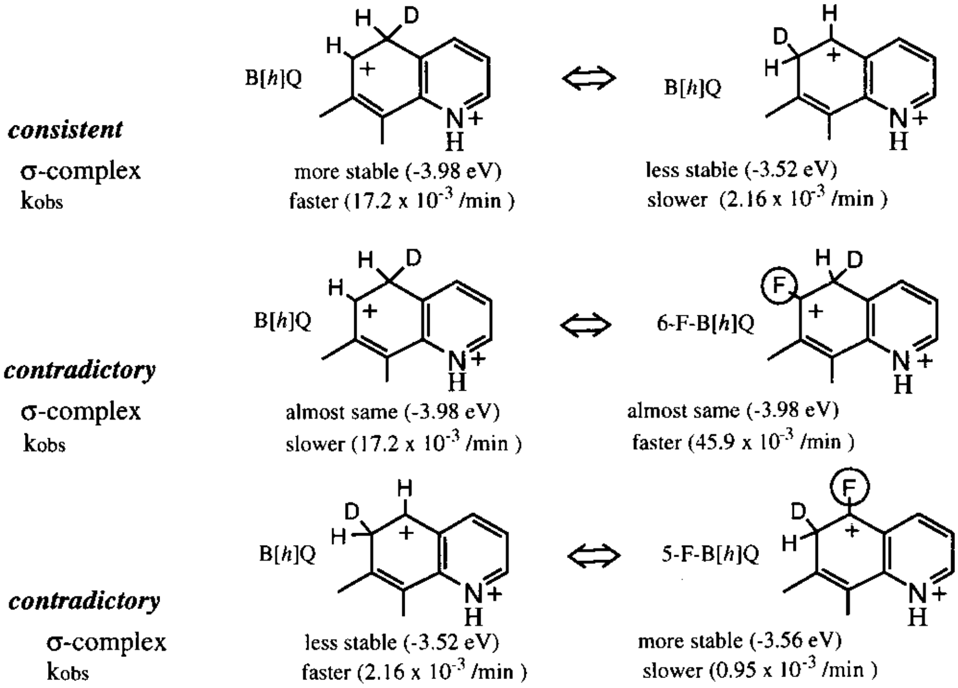
Activation Energy for σ–Complex Formation Estimated by the MO Method of Calculation

The activation energy for σ–complex formation may be semiquantitatively determined by the difference in total energies of the starting B[*h*]Q and its σ–complex. Total energies (sum of electronic energy and core-core repulsion) were therefore calculated by the semiempirical molecular orbital MOPAC 93 PM3 method. The k_{obs} values were plotted *versus* the calculated energy differences between the starting B[*h*]Q's and their corresponding σ–complexes as shown in Figure 1, where the total energy of the protonated cationic structures of the parent B[*h*]Q's was used since deuteration of quinoline and *N*-methylquinolinium ion proceeded at a similar rate for each hydrogen under the same reaction conditions as that employed in the present study (data not shown). The exchange rates of non-exchangeable hydrogens are plotted on the X-axis of Figure 1 which provides an overview of the data. It is suggested that the k_{obs} value could basically be correlated with the energy for σ–complex formation, however, the MO calculation employed here is not sufficiently reliable to quantitatively predict the rate. For examples of individual correlations, as shown in Scheme 2, relative rate of 5-H to that of 6-H of B[*h*]Q, both of which are σ–complexes in the K-region, seems to be satisfactorily reflected by relative stability of these types of complexes. Thus a phenylmethyl cation involved in the σ–complex at position-5 must be more stable than a pyridylmethyl cation in the complex at position-6, as predicted by MO calculation, because of the electron-withdrawing nature of the pyridine nucleus. On the other hand, with regard to



With regard to non-exchangable hydrogens, rates which are assumed to be less than 0.0001/min, are plotted on the x-axis of Figure 1, marked with ▲'s.

Figure 1 *Pseudo-First Order Rate Constants vs. Energy Gains by σ–Complex Formation Starting from B[h]Q's* the fluorinated derivatives, 5-F-B[*h*]Q and 6-F-B[*h*]Q, although MO calculation predicted that 6-F does not affect the stability of the pyridylmethyl cation, 5-H of 6-F-B[*h*]Q underwent deuteration 2.6 times faster than that of the parent B[*h*]Q. MO calculation predicted that the σ–complex at the position-6 of 5-F-B[*h*]Q is slightly stabilized, whereas the exchange rate of 6-H via such a more stable transition state was 2.3 times slower than that of non-fluorinated B[*h*]Q. At present, the effect of F atom substitution could not be quantitatively predicted to a sufficient degree by MO calculations, and this is likely because quantitative evaluation of the electronic and electric interactions of the F atom with its intra/intermolecular environments remains difficult to achieve.



Scheme 2 *Observed Exchange Rates and Stabilities of the σ-Complexes**

(* The difference in calculated total energies of a derivative in question and its σ-complex.)

EXPERIMENTAL

Materials B[*h*]Q was purchased from Tokyo Chemical Industries Co. Ltd. (Tokyo) and its fluorinated derivatives were prepared in our laboratory.[5] Structures of all preparations were confirmed by nmr, uv, ir, mass spectrometry and elementary analysis. Sulfuric acid-d_2 (96% D_2SO_4) of 99.8% isotope purity was purchased from Merck and Co. Inc. (Rahway, NJ).

Measurement of H-D Exchanged Rates Each sample (*ca.* 3.6 mg/ml) dissolved in 96% D_2SO_4 was sealed in a tube and kept at 80°C for specified periods of time. The mixture was neutralized with powdered K_2CO_3 and extracted with $CHCl_3$. The extract was evaporated and dissolved in DMSO-d_6 and subjected to ^{1}H-nmr analysis. The rate was estimated by measuring the areal intensity of the signals in reference to the internal standard signal of methyl protons of $CH_3SO_3^- K^+$.

MO Calculation Molecular orbital calculation was carried out using MOPAC 93 revision 2 (Stewart, J. J. P. JCPE PO81, JCPE Newsletter, 1995, 6, 76). The calculation program used was PM3 (Stewart, J. J. P. J. Comput. Chem., 1989, 10, 209).

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